EXHIBIT D

American Diabetes Association®

National Center
1660 Duke Street
Alexandria, Virginia 22314
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Fax:703 836-7439
http://www.diabetes.org

To prevent and cure diabetes

and to improve the lives of

all people affected by diabetes.

March 17, 1997

Robert G. Thompson, MD
Clinical Development
Amylen Pharmacenticals
9373 Towne Centre Dr.
San Diego, CA 92121

Dear Dr. Thompson:

Congratulations! It is a pleasure to inform you that your abstract, *Pramlintide, an Analog of Human Amylin Improves Glycemic Control in Patients with Type II Diabetes Requiring Insulin*, has been selected for presentation at the Scientific Sessions of our 57th Annual Scientific Meetings and Sessions to be in Boston, Massachusetts from June 21-24, 1997. Your abstract, No. 0116 , will also be published in the May 1997 supplement issue of *Diabetes*.

Your abstract was selected by the Scientific Sessions Meeting Committee from the over 1,500 abstracts submitted this year. It is currently scheduled to be presented as an oral presentation on Sunday, June 22 from 5:30-5:45 p.m. The room assignment has not been made yet, but will be shortly and we will forward that information to you.

Enclosed are appropriate instructions for your presentation and a Preliminary Program with registration and housing forms. Please complete the forms and return them as soon as possible to the address indicated. Since you will not receive this notification until after the March 14 pre-registration deadline, you will be allowed to register at the rate of $260 for Association members or $395 for non-members. Be sure to return your completed registration form by May 1. The registration form enclosed indicates that you are an abstract presenter.

In the event you are unable to attend the meeting due to unforeseen circumstances, please make arrangements to have a co-author present the abstract. If you are unable to make such arrangements or have any questions, contact Sandy DeVault, Manager, Professional Programs at 703/299-2096.

On behalf of the Scientific Sessions Meeting Committee, I would like to thank you for your contribution and effort.

Sincerely,

Dale L. Greiner, PhD
Chair
Scientific Sessions Meeting Committee

DG:sd
Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Duft, Bradford J. *et al.*		
Serial No.:	08/870,762	Group Art Unit:	1645
Filed:	June 6, 1997	Examiner:	Devi, S.
Title: METHODS FOR TREATING OBESITY			

Commissioner for Patents
Washington, D.C. 20231

RESPONSE

Dear Sir:

This Communication is responsive to the Office Action mailed May 30, 2002. Applicants hereby petition for a three-month extension of time to allow timely filing of this Response up to, and including, December 2, 2002 (given that November 30, 2002, falls on the Saturday preceding that Monday). Enclosed is our check in the amount of $980, as required under 37 C.F.R. §1.17(a) for this Response. If this amount is incorrect, please debit or credit any additional fee(s) that should become due during the pendency of these proceedings to Deposit Account Number 50-1273.

Applicants request that the Examiner enter the substance of this Response.

CERTIFICATE OF MAILING
(37 C.F.R. §1.8a)

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being deposited with the United States Postal Service, via Express Mail, on the date shown below with sufficient postage as first class mail in an envelope addressed to the United States Patent and Trademark Office, Washington, D. C. 20231.

Barbara J. Kielt — December 2, 2002
Barbara J. Kielt — Date

EL573390212US
Express Mail No.

AMENDMENTS

In the Specification

Added Paragraphs

At page 14, after the first full paragraph, insert the following paragraphs:

--Further, amylin agonist analogues useful in the methods of this application include amylin agonist analogues having the following amino acid sequence:

$^{1}A_1$-X-Asn-Thr-^{5}Ala-Thr-Y-Ala-Thr-^{10}Gln-Arg-Leu-
B_1-Asn-^{15}Phe-Leu-C_1-D_1-E_1-$^{20}F_1$-G_1-Asn-H_1-Gly-$^{25}I_1$-J_1-
Leu-K_1-L_1-^{30}Thr-M_1-Val-Gly-Ser-^{35}Asn-Thr-Tyr-Z

wherein:

A_1 is hydrogen Lys, Ser, Ala, des-α-amino Lys, or acetylated Lys;

B_1 is Ala, Ser or Thr;

C_1 is Val, Leu or Ile;

D_1 is His or Arg;

E_1 is Ser or Thr;

F_1 is Ser, Thr, Gln or Asn;

G_1 is Asn, Gln or His;

H_1 is Phe, Leu or Tyr;

I_1 is Ala or Pro;

J_1 is Ile, Val, Ala or Leu;

K_1 is Ser, Pro, Leu, Ile or Thr;

L_1 is Ser, Pro or Thr;

M_1 is Asn, Asp or Gln;

X and Y are independently selected residues having side chains which are chemically bonded to each other to form an intramolecular linkage; and

Z is hydroxy, amino, alkylamino, dialkylamino, cycloalkylamino, arylamino, aralkylamino, alkyloxy, aryloxy or aralkyloxy;

provided that:

(a) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is His, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is Phe, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Ser, and M_1 is Asn;

(b) when A_1 is Lys, B_1 is Ala, C_1 is Ile, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is Leu, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Pro, and M_1 is Asn;

(c) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is Arg, E_1 is Thr, F_1 is Ser, G_1 is Asn, H_1 is Leu, I_1 is Ala, J_1 is Ile, K_1 is Ser, L_1 is Pro, and M_1 is Asn;

(d) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is Asn, H_1 is Leu, I_1 is Pro, J_1 is Val, K_1 is Pro, L_1 is Pro, and M_1 is Asn;

(e) when A_1 is Lys, B_1 is Ala, C_1 is Val, D_1 is His, E_1 is Ser, F_1 is Asn, G_1 is Asn, H_1 is Leu, I_1 is Pro, J_1 is Val, K_1 is Ser, L_1 is Pro and M_1 is Asn; or

(f) when A_1 is Lys, B_1 is Thr, C_1 is Val, D_1 is Arg, E_1 is Ser, F_1 is Ser, G_1 is His, H_1 is Leu, I_1 is Ala, J_1 is Ala, K_1 is Leu, L_1 is Pro and M_1 is Asp;

then one or more of any of A_1 to M_1 is not an L-amino acid and Z is not amino.

Suitable side chains for X and Y include groups derived from alkyl sulfhydryls which may form disulfide bonds; alkyl acids and alkyl amines which may form cyclic lactams; alkyl aldehydes or alkyl halides and alkylamines which may condense and be reduced to form an alkyl amine bridge; or side chains which may be connected to form an alkyl, alkenyl, alkynyl, ether or thioether bond. Preferred alkyl chains include lower alkyl groups having from about 1 to about 6 carbon atoms.

As used herein, the following terms have the following meanings unless expressly stated to the contrary:

The term "alkyl" refers to both straight- and branched-chain alkyl groups. The term "lower alkyl" refers to both straight- and branched-chain alkyl groups having a total of from 1 to 6 carbon atoms and includes primary, secondary, and tertiary alkyl groups. Typical lower alkyls include, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like.

The term "aryl" refers to carbocyclic aromatic groups of 6 to 14 carbon atoms such as phenyl and naphthyl, as well as heterocyclic aromatic groups containing 1 to 3 heteroatoms (nitrogen, oxygen, sulfur, etc.) such as pyridyl, triazolopyrazine, pyrimidine and the like.

The term "aralkyl" refers to an "aryl" group of 6 to 10 carbon atoms directly attached to an "alkyl" group of 1 to 4 carbon atoms and includes for example benzyl, p-chlorobenzyl, p-methylbenzyl, and 2-phenylethyl.

The term "cycloalkyl" refers to cyclic alkyl groups of 5 to 8 carbon atoms.

Biologically active derivatives of the above agonist analogues are also included within the scope of amylin agonist analogues useful in the present invention in which the stereochemistry of individual amino acids may be inverted from (L)/S to (D)/R at one or more specific sites. Also included within the scope of amylin agonist analogues useful in the present invention are the agonist analogues modified by glycosylation of Asn, Ser and/or Thr residues.

Biologically active agonist analogues of amylin which contain less peptide character are also included in the scope of amylin agonist analogues useful in the present invention. Such peptide mimetics may include, for example, one or more of the following substitutions for -CO-NH- amide bonds: depsipeptides (-CO-O-), iminomethylenes ($-CH_2-NH-$), *trans*-alkenes (-CH=CH-), ß-enaminonitriles (-C(=CH-CN)-NH-), thioamides (-CS-NH-), thiomethylenes ($-S-CH_2-$ or $-CH_2-S-$), methylenes, and retro-amides (-NH-CO-).

The above-described amylin agonist analogues form salts with various inorganic and organic acids and bases. Such salts include salts prepared with organic and inorganic acids, for example, HCl, HBr, H_2SO_4, H_3PO_4, trifluoroacetic acid, acetic acid, formic acid, methanesulfonic acid, toluenesulfonic acid, maleic acid, fumaric acid, and camphorsulfonic acid. Salts prepared with bases include, for example, ammonium salts, alkali metal salts (such as sodium and potassium salts), and alkali earth salts (such as calcium and magnesium salts). Acetate, hydrochloride, and trifluoroacetate salts are preferred.

The salts may be formed by conventional means, as by reacting the free acid or base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the ions of an existing salt for another

ion on a suitable ion exchange resin. The above-described amylin agonist analogues include various stereoisomers. In the preferred amylin agonist analogues, the chiral centers on the peptide backbone are all S.--

At page 40, after the last paragraph, please insert the following paragraphs:

--To assist in understanding the present invention, the following further Examples A-N are included and describe the results of a series of experiments therein. The following examples relating to this invention should not, of course, be construed as specifically limiting the invention. Such variations of the invention, now known or later developed, which would be within the purview of one skilled in the art are considered to fall within the scope of the present invention as hereinafter claimed.

EXAMPLE A

Preparation of ^{28}Pro-human-Amylin

Solid phase synthesis of this analogue of human ("h-") amylin using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid hydrofluoric acid ("HF") in the presence of dimethylsulfide and anisole. The ^{28}Pro-h-amylin was purified by preparative HPLC. The peptide was found to be homogeneous

by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: (M+1)/e=3914.

EXAMPLE B

Preparation of ^{25}Pro^{26}Val^{28,29}Pro-h-Amylin

Solid phase synthesis of this amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{25}Pro^{26}Val^{28,29}Pro-h-amylin was purified by preparative HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: (M+1)/e=3936.

EXAMPLE C

Preparation of ^{2,7}Cyclo-[^{2}Asp,^{7}Lys]-h-Amylin

Solid phase synthesis of this amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. ^{2}Asp and ^{7}Lys were introduced with Boc-^{2}Asp(Fmoc)-OH and Boc-^{7}Lys(Fmoc)-OH. Following selective side-chain deprotection with piperidine, the side-chain to side-chain (^{2}Asp-^{7}Lys) cyclization was carried out using

benzotriazol-1yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP reagent). Cyclization was as described in Di Maio, J., *et al.*, J. Med. Chem., 33:661-667 (1990); and Felix, A.M., *et al.*, Int. J. Pept. Prot. Res., 32:441 (1988). The ^{2,7}cyclo-[^{2}Asp,^{7}Lys]amylin-MBHA-resin obtained after cyclization was cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{2,7}cyclo-[^{2}Asp,^{7}Lys]-h-amylin was purified by preparative HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. FAB mass spec: (M+1)/e=3925.

EXAMPLE D

Preparation of des-^{1}Lys-h-Amylin

Solid phase synthesis of des-^{1}Lys-h-amylin (also represented as $^{2-37}$h-amylin) using methylbenzhydrylamine anchor-bond resin and N^{α}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,775.

EXAMPLE E

Preparation of ^{1}Ala-h-Amylin

Solid phase synthesis of ^{1}Ala-h-amylin using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{1}Ala-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,847.

EXAMPLE F

Preparation of ^{1}Ser-h-Amylin

Solid phase synthesis of ^{1}Ser-h-amylin using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{1}Ser-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and

capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^+$=3,863.

EXAMPLE G

Preparation of ^{29}Pro-h-Amylin

Solid phase synthesis of this analogue of human amylin using methylbenzhydrylamine anchor-bond resin and N^a-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The ^{29}Pro-h-amylin was purified by preparative HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^+$=3916.

EXAMPLE H

Preparation of ^{25,28}Pro-h-Amylin

Solid phase synthesis of ^{25,28}Pro-h-amylin using methylbenzhydrylamine anchor-bond resin and N^a-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF

in the presence of dimethylsulfide and anisole. The ^{25,28}Pro-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^+$=3,939.

EXAMPLE I

Preparation of des-^{1}Lys^{25,28}Pro-h-Amylin

Solid phase synthesis of des-^{1}Lys^{25,28}Pro-h-amylin using methylbenzhydrylamine anchor-bond resin and N^a-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{25,28}Pro-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^+$=3,811.

EXAMPLE J

Preparation of des-^{1}Lys^{18}Arg^{25,28}Pro-h-Amylin

Solid phase synthesis of des-^{1}Lys^{18}Arg^{25,28}Pro-h-amylin using methylbenzhydrylamine anchor-bond resin and N^a-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained

by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{18}Arg^{25,28}Pro-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,832.

EXAMPLE K

Preparation of des-^{1}Lys^{18}Arg^{25,28,29}Pro-h-Amylin

Solid phase synthesis of des-^{1}Lys^{18}Arg^{25,28,29}Pro-h-amylin using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{18}Arg^{25,28,29}Pro-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,843.

EXAMPLE L

Preparation of des-^{1}Lys^{25,28,29}Pro-h-Amylin

Solid phase synthesis of des-^{1}Lys^{25,28,29}Pro-h-amylin using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection was carried out by standard peptide synthesis methods. The ^{2,7}-[disulfide]amylin-MBHA-resin was obtained by treatment of Acm-protected cysteines with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization was achieved, the resin and side chain protecting groups were cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{25,28,29}Pro-h-amylin was purified by preparative reversed-phase HPLC. The peptide was found to be homogeneous by analytical HPLC and capillary electrophoresis and the structure was confirmed by amino acid analysis and sequence analysis. The product gave the desired mass ion. FAB mass spec: $(M+H)^{+}$=3,823.

EXAMPLE M

Preparation of des-^{1}Lys^{25}Pro^{26}Val^{28,29}Pro-h-Amylin

Solid phase synthesis of this h-amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection is carried out by standard peptide synthesis methods, and the ^{2,7}-[disulfide]amylin-MBHA-resin obtained by treatment with thallium (III) trifluoroacetate in trifluoroacetic acid. After cyclization is achieved, the resin and side chain protecting groups are cleaved with liquid HF in the presence of dimethylsulfide and anisole. The des-^{1}Lys^{25}Pro^{26}Val^{28,29}Pro-h-amylin is then purified by preparative HPLC.

EXAMPLE N

Preparation of [(D)-^{11}Arg]-Amylin

Solid phase synthesis of this amylin analogue using methylbenzhydrylamine anchor-bond resin and N^{a}-Boc/benzyl-side chain protection is carried out by standard peptide synthesis methods. (D)-^{11}Arg is introduced with Boc-(D)-^{11}Arg(Mtr)-OH. The ^{2,7}-[disulfide]amylin-MBHA-resin, obtained by treatment with thallium (III) trifluoroacetate in trifluoroacetic acid, is cyclized and the resin and side chain protecting groups are cleaved with liquid HF in the presence of dimethylsulfide and anisole. The [(D)-^{11}Arg]-amylin is then purified by preparative HPLC.--

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Reworded Paragraphs

Please reword the paragraph bridging pages 19-20 of the originally filed application as follows:

--The receptor binding assay, a competition assay which measures the ability of compounds to bind specifically to membrane-bound amylin receptors, is described in United States Patent No. 5,264,372, issued November 23, 1993, the disclosure of which is incorporated herein by reference. The receptor binding assay is also described in Example 2 below. A preferred source of the membrane preparations used in the assay is the basal forebrain which comprises membranes from the nucleus accumbens and surrounding regions. Compounds being assayed compete for binding to these receptor preparations with ^{125}I Bolton Hunter rat amylin. Competition curves, wherein the amount bound (B) is plotted as a function of the log of the concentration of ligand are analyzed by the computer, using analyses by nonlinear regression to a 4-parameter logistic equation (INPLOT program; GRAPHPAD Software, San Diego, California) or the ALLFIT program of DeLean et al. (ALLFIT, Version 2.7 (NIH, Bethesda, MD 20892)). Munson and Rodbard, Anal. Biochem. 107:220-239 (1980).--

Please reword the paragraph bridging pages 23-24 of the originally filed application as follows:

--Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters DELTA PREP 3000 system. A C4, C8 or C18 preparative column (10 μ, 2.2 X 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5 μ, 0.46 X 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH_3CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters PICO TAG system and processed using the MAXIMA program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115°C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems BIO-ION 20 mass spectrometer.--

Please reword the second paragraph on page 27 of the originally filed application as follows:

--If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose. They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for example, acacia powder, a non-ionic surfactant (such as a TWEEN), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a TRITON).--

Please reword the first full paragraph on page 34 of the originally filed application as follows:

--To measure ^{125}I-amylin binding, membranes from 4 mg original wet weight of tissue were incubated with ^{125}I-amylin at 12-16 pM in 20 mM HEPES buffer containing 0.5 mg/ml bacitracin, 0.5 mg/ml bovine serum albumin, and 0.2 mM PMSF. Solutions were incubated for 60 minutes at 23°C. Incubations were terminated by filtration through GF/B glass fiber filters (Whatman Inc., Clifton, NJ) which had been presoaked for 4 hours in 0.3% polyethyleneimine in order to reduce nonspecific binding of radiolabeled peptides. Filters were washed immediately before filtration with 5 ml cold PBS, and immediately after filtration with 15 ml cold PBS. Filters were removed and radioactivity assessed in a gamma-counter at a counting efficiency of 77%. Competition curves were generated by measuring binding in the presence of 10^{-12} to 10^{-6} M unlabeled test compound and were analyzed by nonlinear regression using a 4-parameter logistic equation (INPLOT program; GRAPHPAD Software, San Diego).--

Please reword the paragraph bridging pages 35-36 of the originally filed application as follows:

--Muscles were added to 50mL Erlenmeyer flasks containing 10mL of a pregassed Krebs-Ringer bicarbonate buffer containing (each liter) NaCl 118.5 mmol (6.93g), KCl 5.94 mmol (443mg), $CaCl_2$ 2.54 mmol (282mg), $MgSO_4$ 1.19 mmol (143mg), KH_2PO_4 1.19 mmol (162mg), $NAHCO_3$ 25 mmol (2.1g), 5.5mmol glucose (1g) and recombinant human insulin (HUMILIN-R, Eli Lilly, IN) and the test compound, as detailed below. pH at 37° was verified as being between 7.1 and 7.4. Muscles were assigned to different flasks so that the 4 muscle pieces from each animal were evenly distributed among the different assay conditions. The incubation media were gassed by gently blowing carbogen (95% O_2, 5% CO_2) over the surface while being continuously agitated at 37°C in an oscillating water bath. After a half-hour "preincubation" period, 0.5μCi of U-^{14}C-glucose was added to each flask which was incubated for a further 60 minutes. Each muscle piece was then rapidly removed, blotted and frozen in liquid N_2, weighed and stored for subsequent determination of ^{14}C-glycogen.—

Please reword the paragraph bridging pages 38-39 of the originally filed application as follows:

--Gastric emptying was measured using a modification (Plourde et al., Life Sci. 53:857-862 (1993)) of the original method of Scarpignato et al. (Arch. Int. Pharmacodyn. Ther. 246:286-295 (1980)). Briefly, conscious rats received by gavage 1.5 mL of an acoloric gel containing 1.5% methyl cellulose (M-0262, Sigma Chemical Co., St. Louis, MO) and 0.05% phenol red indicator. Twenty minutes after gavage, rats were anesthetized using 5% halothane, the stomach exposed and clamped at the pyloric and lower esophageal sphincters using artery forceps, removed and opened into an alkaline solution which was made up to a fixed volume. Stomach content was derived from the intensity of the phenol red in the alkaline solution, measured by absorbance at a wavelength of 560 nm. In most experiments, the stomach was clear. In other experiments, particulate gastric contents were centrifuged

to clear the solution for absorbance measurements. Where the diluted gastric contents remained turbid, the spectroscopic absorbance due to phenol red was derived as the difference between that present in alkaline vs acetified diluent. In separate experiments on 7 rats, the stomach and small intestine were both excised and opened into an alkaline solution. The quantity of phenol red that could be recovered from the upper gastrointestinal tract within 29 minutes of gavage was 89 ± 4%; dye which appeared to bind irrecoverably to the gut luminal surface may have accounted for the balance. To compensate for this small loss, percent of stomach contents remaining after 20 minutes were expressed as a fraction of the gastric contents recovered from control rats sacrificed immediately after gavage in the same experiment. Percent gastric emptying contents remaining = (absorbance at 20 min)/(absorbance at 0 min). Dose response curves for gastric emptying were fitted to a 4-parameter logistic model using a least-squares iterative routine (ALLFIT, v2.7, NIH, Bethesda, MD) to derive ED_{50}s. Since ED_{50} is log-normally distributed, it is expressed ± standard error of the logarithm. Pairwise comparisons were performed using one-way analysis of variance and the STUDENT-NEWMAN-KEULS multiple comparisons test (INSTAT v2.0, GRAPHPAD Software, San Diego, CA) using $P < 0.05$ as the level of significance.—

Please add the following new claims 7-16:

7. (New) A method of treating obesity in a human subject comprising administering to said subject an amount of a composition comprising an amylin or an amylin agonist effective to treat obesity, with the proviso that the composition does not contain a cholecystokinin or a cholecystokinin agonist.

8. (New) The method of claim 1, 2 or 3 wherein said treatment of obesity of said subject comprises administration of said effective amount of an anti-obesity agent consisting of an amylin or an amylin agonist for at least about four weeks.

9. (New) A method according to claim 1, 2 or 3 wherein the composition comprising an effective amount of an anti-obesity agent consisting of an amylin or amylin agonist is administered QID in an amount of 30 μg/dose.

10. (New) A method according to claim 1, 2 or 3 wherein the composition comprising an effective amount of an anti-obesity agent consisting of an amylin or amylin agonist is administered TID or QID in an amount of 60 μg/dose.

11. (New) A method according to claim 1, wherein the composition comprising an effective amount of an anti-obesity agent consisting of an amylin or an amylin agonist is administered in an amount of about 0.01 milligrams per day to about 5 milligrams per day.

12. (New) A method according to claim 1, wherein the composition comprising an effective amount of an anti-obesity agent consisting of an amylin or amylin agonist is administered in an amount of about 0.05 milligrams per day to about 2 milligrams per day.

13. (New) A method according to claim 1, wherein the composition comprising an effective amount of an anti-obesity agent consisting of an amylin or amylin agonist is administered in an amount of about 0.1 milligrams per day to about 1 milligram per day.

14. (New) A method of treating obesity in a human subject comprising administering to said subject a composition comprising a compound selected from the group consisting of amylins, amylin agonists, and pharmaceutically acceptable salts thereof.

15. (New) The method of claim 1, 2 or 3, wherein the weight of said human subject is lower following four weeks of treatment.

16. (New) A method of treating obesity in a human subject comprising administering to said subject an effective amount of a composition consisting essentially of an amylin or an amylin agonist.

REMARKS

Claims 1-6 remain pending in the application, with new claims 7-16 added. In accordance with 37 C.F.R. §1.121, a marked up copy of the specification paragraphs and claims is appended hereto. Additional language included with this Response is noted by underlining. Language that has been deleted is noted by bracketing.

Before discussing the rejections that were entered in the case, Applicants first mention the pending claims and address art teaching way from the invention. Applicants also describe further background information regarding obesity, treatment of obesity, gastric emptying, and amylin. As the court noted in *In re Cable*, 347 F.2d 872, 878, 146 USPQ 175, 180 (1965), "Where affirmative evidence is of record bearing on the history of an art, it should be considered and given appropriate weight in arriving at an 'objective' vis-a-vis a 'subjective' determination of the issues arising under 35 U.S.C. 103." A Supplemental Information Disclosure Statement will be filed to provide the PTO with non-patent documents referred to herein that are not already of record.

Pending Claims

The instant application describes weight reduction, and discloses and claims methods directed to the treatment of obesity by administration of an effective amount of a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist, and claims priority to an application first filed on June 6, 1997, over five years ago. Various dependent claims relate to administration of an amylin agonist analogue (claim 2) and to the amylin agonist known as "pramlintide", *i.e.*, ^{25,28,29}Pro-h-

amylin (claim 3). Other dependent claims relate to subcutaneous administration of an amylin or amylin agonist for the treatment of obesity (claim 4), and to the frequency of administration and/or dosages thereof (claims 5and 6). For example, claim 5 defines the administration of an amylin or an amylin agonist from 1 to 4 times per day for the treatment of obesity. Claim 6 (which depends from claim 5) defines the administration of an amylin or an amylin agonist in an amount from about 30μg per dose to about 300μg per dose.

The Art Teaches Away From the Claimed Invention

U.S. Patent No. 5,739,106 to Rink *et al.*, which is assigned to Amylin Pharmaceuticals, Inc., assignee of the instant application, refers at column 7, lines 4-6, to a report "that amylin, when administered IP [intraperitoneal] in rats at a dosage of 0.5 μg/kg, significantly decreased food intake," citing *Lutz et al.*, Physiology & Behavior 55:891-895 (1994). Notably, however, the Rink *et al.* '106 patent is in fact contrary to the report of Lutz *et al.* and teaches away from the instant invention for at least two reasons.

First, the Rink *et al.* patent teaches that intraperitoneal (IP) injection of 1.0 μg/kg of amylin – twice the IP dose reported to have been administered in the 1994 Lutz *et al.* article – had "no measurable effect on food intake" (col. 7, lines 18-20; emphasis added).

Second, the '106 patent teaches that the useful reduction in food intake described by Rink *et al.* was only upon administration of both an amylin agonist with a cholecystokinin agonist.[1] Stating that IP

[1] *See, e.g.*, claim 1 (a "composition comprising an amylin agonist and a CCK agonist admixed in a pharmaceutically acceptable carrier"), claim 7 ("A method for reducing food intake in a mammal comprising administering to said mammal an effective food intake-reducing combination of an amylin agonist and a CCK agonist"), claim 8 ("A method for the control of appetite in a mammal comprising co-administering to said mammal therapeutically effective amounts of an amylin agonist and a CCK agonist"), and claim 9 ("A method for the control of body weight of a subject comprising co-

injection of either 1.0 μg/kg of CCK-8 or 1.0 μg/kg of amylin had "no measurable effect on food intake," the patent goes on to report that, surprisingly, "administration of 1.0 μg/kg of each peptide causes a substantial reduction of food intake about equivalent to that seen with 100 μg/kg of either peptide alone" (col. 7, lines 20-23; emphasis added).

This finding was unquestionably surprising given, for example, the unpredictable state of the art. For example, Rink *et al.* indicates in col. 6, lines 40-44, that "it has been proposed that excess amylin is associated with obesity, and that obesity may be treated with amylin antagonists. U.S. Pat. No. 5,280,014, issued Jan. 18, 1994" (emphases added). While the Rink *et al.* '106 patent appears to be the first to report a successful, useful application of amylin agonist compounds in the reduction of food intake, that achievement was only seen when it was co-administered with a cholecystokinin agonist.

Thus, Rink *et al.* teaches away from the claimed invention. The Rink *et al.* patent states that reduction of food intake with both an amylin agonist and a cholecystokinin agonist was "about equivalent to that seen with 100 μg/kg of either peptide alone." Calculating a corresponding dose for humans, Applicants note that a single 100 μg/kg dose of a compound in a 70 kilogram human equates to a dose of about 7000 μg, or 7 mg (and a dose of about 9000 μg, or 9 mg for a typical, 90 kilogram overweight human). Thus, the referenced 100 μg/kg bolus administration of rat amylin is significantly higher than the highest daily doses of an amylin or amylin agonist described in the instant application. *See, e.g.*, page 27, line 17, to page 28, line 10, of the pending application, which describes daily doses

administering to said subject an effective food intake-reducing combination of an amylin agonist and a CCK agonist"). (All emphases added.) *See also* claims 17-82 directed to "hybrid peptides", which "incorporate features of amylin agonist peptides and CCK agonist peptides, wherein such hybrid peptides feature an amylin agonist peptide covalently linked to a CCK agonist peptide" as well as other hybrid peptide compounds, "some of which employ linkers, and which incorporate various features of amylin agonists and CCK agonists."

from about 0.01 to about 5 mg per day, preferably about 0.05 to about 2 mg per day, and more preferably about 0.1 to 1 mg per day.

Additionally, a 100 μg/kg dose of rat amylin is between 30-60 times higher than the highest dose of amylin agonist administered to humans in, for example, the studies in Examples 1 and 2 of the instant application (30 μg QID, *i.e.*, 120 μg or 1.7 μg/kg for a 70 kilogram subject; 60 μg TID, *i.e.*, 180 μg or 2.6 μg/kg for a 70 kilogram subject; and, 60 μg QID, *i.e.*, 240 μg or 3.4 μg/kg for a 70 kilogram subject (page 29, lines3-9)).[2] Given the potential of amylin to cause transient nausea, furthermore, it is likely that any food intake reduction seen in experimental animals following an IP bolus injection of 100 μg/kg amylin as indicated in the Rink *et al.* '106 patent was due to the fact that the animals became sick. It is also noted that there is no indication in Rink *et al.* that administration of 100 μg/kg of amylin led to a reduction of body weight useful for treating obesity.

Applicants also note that motivation to arrive at the claimed invention was not known prior to the present invention based on assertions regarding articles proposing an effect of amylin on food intake. Applicants also refer the Examiner, for example, to a 1997 article by Lutz *et al.*, "Evidence for a physiological role of central calcitonin gene-rlated peptide (CGRP) receptors in the control of food intake in rats," *Neuroscience Letters* **230**:159-162 (1997). In this paper, Lutz *et al.* summarized art regarding amylin and food intake. Referring to the findings in fourteen articles spanning 1991 to 1996 (including the Lutz *et al.* article cited in the Rink '106 patent, as well as the Morley (1991) and Arnelo (1996) documents cited by the PTO) the authors stated that "no clear evidence has been brought forward

[2] Assuming administration to a typical overweight human weighing 90 kilograms, furthermore, a 100 μg/kg dose of rat amylin is between 37-80 times higher than the highest doses of amylin agonist administered to human subjects in the experiments of Examples 1 and 2 (30 μg QID, *i.e.*, 120 μg or 1.3 μg/kg for a 90 kilogram subject; 60 μg TID, *i.e.*, 180 μg or 2.0 μg/kg for a 90 kilogram subject; and, 60 μg QID, *i.e.*, 240 μg or 2.7 μg/kg for a 90 kilogram subject).

so far establishing endogenous amylin or CGRP as endogenous satiety peptides" (emphasis added). In fact, it was not until the year 2000 that the Lutz *et al.* group sought to investigate the "hypothesis" that amylin "serves as an adiposity signal acting within the brain to regulate long-term food intake, body weight and adiposity" and, following analysis of the results of a study on the effects of amylin infusion directly into the brain, concluded that the information from this study may "ultimately be applied to strategies of treatment and prevention of disorders of body weight regulation." Rushing, P.A., Hagan, M.M., Seeley, R.J., Lutz, T.A. and Woods, S.C., "Amylin: A Novel Action in the Brain to Reduce Body Weight," *Endocrinology* 141 (2):850-853 (2000). Indeed, it was not until the year 2001 that the Lutz *et al.* group reported their investigation into the "physiological relevance" of the hypothesis that amylin "serves as an adiposity signal acting within the brain to regulate long-term energy balance" and, following analysis of the results of a study on the effects of the amylin antagonist AC187 in which they report findings "consistent with the hypothesis that central actions of endogenous amylin contribute to the long-term regulation of energy balance," stated for the first time that:

> In conclusion, these findings are new to the literature and provide strong support for the involvement of central actions of endogenous amylin in the regulation of long-term energy homeostasis. Together with the results of our previous report [from *Endocrinology* 141 (2):850-853 (2000)], the current data indicate that amylin may prove to be an important target in the treatment of obesity [emphases added].

Rushing, P.A., Hagan, M.M., Seeley, R.J., Lutz, T.A., D'Alessio, D.A., Air, L. and Woods, S.C., "Inhibition of Central Amylin Signaling Increases Food Intake and Body Adiposity in Rats," *Endocrinology* 142 (11):5035-5038 (2001).

Applicants also submit that there is also no basis for discounting or ignoring the teaching away that is evident from U.S. Patent Nos. 5,280,014 and 5,364,841, both entitled "Treatment of obesity and essential hypertension and related disorders," and both of which teach from top to bottom, completely

and unswervingly away from the instant invention in describing the use of amylin antagonists – not agonists – to treat obesity.[3] Whether considered in whole or in part, the '014 and '841 anti-obesity patents both teach the use of amylin antagonist compounds. Nowhere does either patent state or suggest any use for amylin agonists in the treatment of obesity.

In re Caldwell, 319 F.2d 254, 256, 138 USPQ 243, 245 (CCPA 1963) provides that a reference teaches away if it leaves the impression that the product would not have the property sought by the applicant. *Accord In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). The claims of the instant application are directed to the use of amylins and amylin agonists for treating obesity, while the 5,280,014 and 5,364,841 patents both teach the use of amylin antagonists for the same purpose. Thus, these patents teach away from the invention because they leave the impression that Applicants' amylin agonist products would not have the property taught by the '014 and '841 patents – amylin antagonism. The law has long provided that "teaching away" from a claimed invention by alleged prior art is an important indicium of non-obviousness that cannot be ignored. *E.g., In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988) ("Evidence that supports, rather than negates, patentability must be fairly considered."); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449, 230 USPQ 416 (Fed. Cir.) (cannot ignore art teaching away

[3] *See, e.g.*, the "Summary of the Invention," which states, in pertinent part:

> "The present invention is directed to the use of amylin . . . receptor blockers and antagonists as treatments for obesity and essential hypertension, . . . whereby amylin . . . antagonists and blockers are utilized to decrease the action of amylin . . . . . The action of the amylin . . . blockers increases the uptake of glucose into skeletal muscle, smooth muscle and liver, especially by counteracting the effects of amylin to increase hepatic glucose output and to reduce the rate of hexose uptake into muscle and liver cells, and also by counteracting the effect of amylin to reduce the rates of incorporation of glucose into glycogen. This action reverses the effect of amylin . . . to promote the storage of energy as fat, and increases the amount of glucose transported into muscle and liver cells. Amylin blockers will therefore act as anti-obesity . . . agents, . . . [all emphases added]."

from claimed invention), *cert. denied*, 484 U.S. 823 (1987). *See also, e.g., United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966) ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness"); *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 961, 220 USPQ 592 (Fed. Cir. 1983) (teaching away from the prior art supports a conclusion of nonobviousness); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550-51, 220 USPQ 303, 311 (Fed. Cir. 1983) (the totality of a reference's teachings must be considered), *cert. denied*, 469 U.S. 851 (1984).

Applicants also note the multiple references in the Office Action to those "skilled in the art" and what they would allegedly have been motivated to do. *See, e.g.*, May 30, 2002 Office Action at pages 14, 15, 17, 19 and 21. First, the statutory mandate is directed to those of "ordinary skill in the art." The PTO analyses referring to those "skilled in the art" are defective for this reason alone. The language of section 103 requires evaluation of obviousness from the perspective of a person of ordinary skill in the art at the time the invention was made. *E.g., Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Hybritech, Inc. v. Monoclonal Antibodies, Inc .*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987). The critical step is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *E.g.*, W.*L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). Applicants refer the PTO to, for example, *Hybritech Inc. v. Abbott Labs*, 4 U.S.P.Q.2d 1001, 1008-09, *aff'd* , 849 F.2d 1446, 7 USPQ2d 1191 (Fed. Cir. 1988). In that case, the court emphasized that those of ordinary skill are not "persons of superior skill, intellect and insight," or those who are skilled in remote arts or geniuses in the field (citing *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697,

218 USPQ 865 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043, 104 S.Ct. 709, 224 USPQ 520 (1984)). Instead, said the court, one must look to "those in the 'trenches,' actually attempting to produce commercial products." *Id.* at 1009. As Judge Rich emphasized in *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454, 227 USPQ 293, 297-98 (Fed. Cir. 1985), however, the law is very clear that:

> The issue of obviousness is determined entirely with reference to a hypothetical "person having ordinary skill in the art." It is only that hypothetical person who is presumed to be aware of all the pertinent art. The actual inventor's skill is irrelevant to this inquiry, and this is for a very important reason. The statutory emphasis is on a person of ordinary skill. Inventors, as a class, according to the concepts underlying the Constitution and the statutes that have created the patent system, possess something -- call it what you will -- which sets them apart from the workers of ordinary skill, and one should not go about determining obviousness under § 103 by inquiring into what patentees (*i.e.*, inventors) would have known or would likely have done, faced with the revelation of references. A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which. [Emphasis by the court.]

Judge Rich also stressed that, "A person of ordinary skill in the art is also presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate, whether by patient, and often expensive, systematic research or by extraordinary insights, it makes no difference which." *Id.*

In any event, Applicants remind the PTO individuals skilled in the art, the scientist-inventors named on the Rink *et al.* '106 patent, taught the art that injection of 1.0 μg/kg of amylin had "no measurable effect on food intake," and revealed that a treatment for reduction in food intake based only upon administration of an amylin agonist together with a cholecystokinin agonist. This enhances the evidentiary value of the Rink *et al.* '106 patent as an out-and-out objective indicium of nonobviousness.

It also plainly enhances the significance that should be attached to the beneficial result of amylin agonism for the treatment of obesity as described and claimed by Applicants, and diminishes the evidentiary value placed by the PTO on the notion that one of ordinary skill in the art would have been motivated to make Applicants' compositions and to use them to effect amylin agonism for treatment of obesity. Indeed, the '106 patent states that, "Giving regard to amylin's effects on muscle, liver and adipose tissue, it has been proposed that excess amylin is associated with obesity, and that obesity may be treated with amylin antagonists. U.S. Pat. No. 5,280,014, issued Jan. 18, 1994" (emphases added).

Contradictory publications cannot be combined to make an obvious rejection under Section 103. *See In re Wynne*, 133 USPQ 517, 519-520 (CCPA 1962) (Rich, J.) ("All these references amount to is two disclosures of different fire polishing methods which are contradictory and neither of which suggests doing it in the manner or with the apparatus disclosed and claimed by appellant."). Thus, although initial rejections based on the 5,280,014 and 5,364,841 amylin antagonist/anti-obesity patents as a result of the misapprehension of the nature of CGRP 8-37 have since been withdrawn, Applicants note the PTO's further statement at pages 5-6 of the June 5, 2002 Office Action – namely, that "one would be motivated to make use of amylin agonists . . . to treat body weight, particularly since several published reports at the time had already taught an appetite suppressing or anorexia-causing role for amylin" – does not hold up.

Obesity is a Complex and Multifactorial Disease That Has Been the Subject of Decades of Research

Any inquiry into nonobviousness is aided by the existence of objective evidence of patentability. This can include the failure of others, long felt need, movement of the skilled in a different direction or directions, *etc.*, as well as "other events proved to have actually happened in the real world (hence the

description 'objective')." *Panduit Corp. v. Dennison Manufacturing Co.*, 810 F.2d 1561, 1569, 1 USPQ2d 1593, 1598 (Fed. Cir. 1987). Such evidence is, in the words of Judge Rich, "circumstantial evidence of the highest probative value." Rich, *Laying the Ghost of the "Invention" Requirement*, in Nonobviousness – The Ultimate Condition of Patentability 1:501, 513 (J. Witherspoon ed. 1978).

Thus, following the mandate of the Federal Circuit in *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1544, 221 USPQ 1 (Fed. Cir. 1984), relevant inquiries must be directed to the "real world" surrounding the patent application. As noted in the application and herein, the "real" factors enumerated by the Federal Circuit – the deficiencies of the prior art, long-felt need, and so on, as well as teaching away and movement of the skilled in a different direction and contradictions and confusion in the art, are all present in this case and tell strongly against a conclusion of obviousness. "Obviousness" cannot determined by attempts to reconstruct an invention with pinpoint selections from reams of alleged prior art, using the specification as a guide years after it has been revealed to the world by the inventors.

As a major health problem that recently has reached epidemic proportions in the United States, Europe and other countries, it is reported that obesity accounts for substantial morbidity and mortality and has a profound negative impact on health-related quality of life. The health implications of obesity are so serious that obesity has been designated a major cause of death in the United States. *See* National Institutes of Health, National Heart, Lung, and Blood Institute, "Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report," *Obes. Res.* 1998;6(suppl 2):51S-209S. *See also* Popkin and Doak, "The Obesity Epidemic Is a Worldwide

Phenomenon," *Nutrition Reviews* 56(4):106-114 (Apr 1998); Must, *et al.*, "The Disease Burden Associated With Overweight and Obesity," *JAMA* 282(16): 1523-1529 (October 27, 1999).

It is also understood that obesity is a complex clinical condition. The National Institutes of Health stated in 1998 that, "Obesity is a complex multifactoral chronic disease that develops from an interaction of genotype and the environment. Our understanding of how and why obesity develops is incomplete, but involves the integration of social, behavioral, cultural, metabolic and genetic factors." Likewise, the August, 1993 edition of the *Journal Of The American Medical Association* observed that "...obesity is a heterogeneous disorder and its causes are incompletely understood." According to another report in 1999, a variety of social, behavioral, cultural, environmental, physiological and genetic factors contribute to obesity. Beers, *et al.*, "Obesity: the excessive accumulation of body fat." The Merck Manual of Diagnosis & Therapy [Merck Web site]. Whitehouse Station, New Jersey: Merck & Co., Inc, 1999. Available at http://www.merck.com/pubs/mmanual/section1/chapter5/5a.htm (accessed Oct 15, 2002). Not only may obesity involve considerations of energy intake (including food intake and regulation of food intake by the brain), but genetics, energy expenditure (including voluntary energy expenditure, resting energy expenditure, and diet-induced thermogenesis), effects of dietary composition, psychological factors (including psychopathology and seasonal affective disorder (SAD)), as well as endocrinological factors (including effects of the thyroid, adrenals, ovaries and testes, and the endocrine pancreas). Additional complications result from various known co-morbidities, including atherosclerotic diseases, coronary artery disease, sleep apnea, and type 2 diabetes.

In light of the seriousness and the complexity of the disease, many medical strategies have been or are being attempted, and efforts over the years to identify useful remedies for obesity have occupied a

great deal of effort by many individuals and companies throughout the world.[4] These include, for example, dietary treatments, behavior modification, exercise, jaw wiring, stomach surgery (including gastric bypass and gastroplasty), jejunoileal bypass surgery, regional fat removal, and caloric dilution (including high fiber diets, fat substitutes, and artificial sweeteners).

With obesity affecting more than one third of Americans and more than one half of certain populations (*e.g.*, Hispanic females), its important role in overall morbidity and mortality is clear. While recognition of the problem is straightforward, treatment is not. Thus, in addition to the above strategies, various pharmaceutical therapies have also been theorized or implemented. A 2002 *New England Journal of Medicine* review of the pharmacotherapy of obesity, which includes a discussion of clinical trials of investigational weight-loss agents, may be found in Yanovski SZ, Yanovski JA, "Obesity," *N Engl J Med* February 21, 2002;346:591-602. According to the authors, pharmacotherapy for weight loss falls primarily into two categories, (1) appetite suppressants and (2) agents that decrease food absorption (*see id.* at Table 1 on page 593, entitled "Medications Approved for the Treatment of Obesity").

Noradrenergic agents (*e.g.*, phentermine and mazindol) are approved by the U.S. Food and Drug Administration (FDA) for short-term adjunctive treatment of obesity. Agents that raise serotonin levels have been used in weight loss management but are reported to have serious side effects (*e.g.*, fenfluramine, which was withdrawn from the market because it caused valvular heart disease, as discussed further *infra*) or lack long-term efficacy (*e.g.*, fluoxetine and other selective serotonin reuptake

[4] Hundreds of millions of dollars are spent each year on obesity research in the United States alone. According to the American Obesity Association, "Sources of research funding are typically the government, pharmaceutical companies, universities and other research organizations, and the government, through the National Institutes of Health, invests about $168 million on obesity research. At the same time, reports the AOA, "Pharmaceutical companies also invest millions in trying to find a drug or therapy. That may sound like enough money, but it isn't nearly" (http://www.obesity.org/subs/aoaresearch).

inhibitors). Sibutramine is a mixed noradrenergic-serotonergic agent. Sibutramine produces its weight-reducing effects by inhibiting norepinephrine, serotonin, and dopamine re-uptake. Its more common side effects included dry mouth, constipation, headache, and insomnia. Although it has not been associated with valvular heart disease, because sibutramine substantially increases blood pressure in some patients, regular monitoring of blood pressure is required in patients for whom the drug is prescribed. Because sibutramine is also associated with increases in heart rate, it not recommended for use in patients with a history of coronary artery disease, congestive heart failure, cardiac arrhythmias, or stroke.

The only FDA-approved medication to decrease food absorption is orlistat ("Xenical®"). Orlistat is a lipase inhibitor that acts by inhibiting the absorption of dietary fats. "The third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III)," *JAMA* **2001**;285(19):2486-2497. Because malabsorption of dietary fat is responsible for the weight loss effect of this agent, the typical side effects include flatulence, and increased stool frequency and urgency. Blackburn, G.L., "Managing Obesity In America: An Overview," *Advanced Studies in Medicine* Vol. 2, No. 2, pages 40-49 (January 2002).

The Yanovski and Yanovski article states that the "safety and efficacy of weight-loss medications beyond two years of use have not been established." *Id.* at 600. Thus, while there are several drugs available by prescription to facilitate weight loss, only two have been approved by the Food and Drug Administration (FDA) for prolonged use; orlistat (Xenical) and sibutramine (Meridia).

Blackburn, G.L., "Managing Obesity In America: An Overview," *Advanced Studies in Medicine* Vol. 2, No. 2, pages 40-49 (January 2002). *See also* "AACE/ACE Position Statement on the Prevention, Diagnosis and Treatment of Obesity (1998 Revision), Endocrine Practice 4(5):297 at pages 315-319 (available at http://www.aace.com).

More pharmaceutical therapies have been hypothesized as opposed to actually implemented. See, for example, the 1998 summary of potential obesity drugs and targets in Campfield *et al.*, "Strategies and Potential Molecular Targets for Obesity Treatment, *Science* 280:1383-1387 (29 May 1998), which references the following "Potential targets for new anti-obesity drugs" but contains no mention of amylin or amylin agonists: (1) serotonin re-uptake inhibitors; (2) norepinephrine re-uptake inhibitors; (3) dopamine re-uptake inhibitors; (4) OB receptor agonists; (5) NPY receptor (Y5, Y1) antagonists; (6) MC4 receptor agonists; (7) agouti-related peptide agonists; (8) PMOC antagonists; (9) MCH receptor antagonists; (10) CRH receptor/CRH binding protein antagonists; (11) urocortin antagonists; (12) galanin receptor antagonists; (13) orexin/hypocretin antagonists; (14) CCK-A receptor agonists; (15) GLP-1 receptor agonists; (16) bombesin agonists; (17) UCP2/UCP3 stimulators; (18) PKA stimulators; (19) β–3 adrenergic receptor agonists; and, (20) GH receptor agonists. Applicants also refer the PTO to Curzon and Gibson, entitled "Pharmacological Treatment of Obesity" (published in 2000 and available at www.acnp.org/g4/GN401000156/CH152.html), which also contains no mention of amylin or amylin agonists. In other words, there is no single biochemical pathway, mechanism, or molecular target for pharmacological intervention that is believed by those skilled in the art to be likely lead to new treatments. This constitutes objective evidence of, for example, the movement of those of skill and ordinary skill alike in a different direction or directions, and is indicative of nonobviousness.

Clearly, there is a tremendous potential market for drugs of to treat obesity. Total costs in the United States for all obesity-related health problems are estimated at greater than $200 billion per year. It has been reported that "conservative estimates" for the obesity drug market in the United States are greater than $5 billion by the year 2005 and greater than $10 billion by 2010, "if suitable drugs are available during that period." Kordik and Reitz, "Pharmacological Treatment of Obesity: Therapeutic Strategies," *Journal of Medicinal Chemistry* Vol. 42, No. 2, pages 181-201 (January 28, 1999). Thus, agents that reduce body weight have been actively sought after for many decades. According to the American Obesity Association, however, "Research on obesity is desperately needed" (http://www.obesity.org/subs/aoaresearch). If modulation of gastric emptying was the cure for all things relating to obesity and weight reduction, as proposed by the PTO, it would be the basis for treatment. To be sure, it is not.

The PTO's Reliance on Cited Literature Said to Relate to Gastric Emptying is Misplaced

Notwithstanding decades of extensive efforts and the myriad and diverse attempts to identify treatments that would relieve the worldwide epidemic of obesity by industry, academic and government researchers throughout the world, only a small number have been approved to date, and none are based on delaying gastric emptying. The May 30, 2002 Office Action in this case, however, is based on a simple theme that is not reflective of the specific art to which it relates, the vastness or complexity of that art, or an understanding of unsolved problems that persist in the art. *See Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45, 43 S.Ct. 322, 67 L.Ed. 523 (1923). Referencing only a small selection of the thousands of patents and publications over decades of research dealing with obesity, and more than a decade of amylin research, the PTO's alleged *prima facie* case of obviousness springs from the following stark syllogism, namely:

1. that amylin is allegedly a "peripheral anorectic peptide" (citing Morley *et al.* (1993), but not taking into account, among other things, U.S. Pat. No. 5,656,590 issued August 12, 1997 to Rink *et al.* on an application filed on November 24, 1993 for "Treatment of anorexia and related states," which describes use of amylin and amylin agonists in order to "increase adipose tissue in such patients," or the 1997 Lutz *et al.* paper stating that "no clear evidence has been brought forward so far establishing endogenous amylin . . . as [an] endogenous satiety peptide[]" (*Neuroscience Letters* **230**:159-162 (1997));

2. that amylin agonists such as pramlintide have "anti-gastric emptying properties" (citing, for example, MacDonald *et al.* (August 1995) and Kong *et al.* (January 1997), but taking no notice of articles reporting that obesity is characterized by delayed rather than accelerated gastric emptying (footnotes 7 and 8, *infra*));

3. that pramlintide has "anti-hyperglycemic effects" (citing 1996's Kolterman *et al.* (WO/96/40220)); and,

4. therefore, says the PTO, based on the further allegation of an "express suggestion" in the art that any and all "anorectic and anti-gastric emptying agents are desirable as anti-obesity agents" (citing two more documents, Frishman *et al.* (1997) and Weintraub *et al.* (1989), but again ignoring articles stating that gastric emptying and the lack of relation to obesity) the "instant claims" are *prima facie* obvious.

It has been pointed out that art that may be relied on by the PTO constitutes only those items that one of ordinary skill in the art would have selected without the advantage of hindsight or knowledge of the invention. *Union Carbide Corporation v. American Can Company*, 724 F.2d 1567, 220 USPQ 584,

591 n.6 (Fed. Cir. 1984); *In re Antle*, 444 F.2d 1168, 170 USPQ 285 (CCPA 1971). The Federal Circuit has repeatedly cautioned against employing hindsight by using applicants' disclosure as a blueprint to reconstruct the claimed invention out of isolated teachings of the alleged prior art. *E.g., Grain Processing Corp. v. American Maize-Products Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788, 1792 (Fed. Cir. 1988); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."); W.*L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (The problem with combining references using hindsight to render a claimed invention obvious is that it "simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability."). That mandate has not been complied with by the PTO here.

To ascertain the scope of the prior art, furthermore, the PTO must examine "the field of the inventor's endeavor," *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 758 F.2d 613, 620, 225 USPQ 634, 638 (Fed. Cir. 1985), and "the particular problem with which the inventor was involved," *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983), at the "time the invention was made," *see* 35 U.S.C. Section 103(a). The PTO has apparently defined the problem as merely identifying any allegedly "anorectic" or "anti-gastric emptying agent." With this approach, the PTO has adopted an overly narrow view of the scope of the art, which has in turn led to a failure to recognize and take into account the problems facing the inventors. It also infected the PTO's determinations about the scope and content of the art, which are not taken into account.

The PTO based its conclusion of obviousness in large part on its view that two articles – one from 1989 and another dated nine years later – allegedly showed the desirability of "anorectic and anti-gastric emptying agents . . . as anti-obesity agents." While a "desirability" might provide some indication to one of ordinary skill in the art, the art as a whole must be taken into account in determining the existence of any such desirability, or whether the desirability is of sufficient merit or strength to direct those skilled in the art to a later-made invention. In other words, the existence of such an indication depends on the content of the art, *i.e.*, what the art as a whole would have taught one of ordinary skill in this art at the time of the invention. Not only does that include, in this case, a decade of oftentimes conflicting art relating to amylin (first reported in 1987[5]) and its myriad actions,[6] but decades of art relating to the complexity and intractability of obesity, and years of art relating to gastric emptying to the extent, if any, that it may relate to obesity. As the Federal Circuit has instructed, care must be taken to avoid hindsight reconstruction by using "the [application under review] as a guide through the maze of prior art references" in an effort to achieve the claimed invention. *Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1012, 217 USPQ 193, 199 (Fed. Cir. 1983).

Turning to gastric emptying and the PTO impression that anything that might slow gastric emptying would have been an obvious triumph in the treatment of obesity, in 1975 it was put forward that increased energy density of meals and accelerated gastric emptying may contribute to the development of obesity in some individuals. Hunt J.N., *et al.*, "Energy density of food, gastric

[5] Cooper GJ, *et al.*, "Purification and characterization of a peptide from amyloid-rich pancreases of type 2 diabetic patients," *Proc Natl Acad Sci U S A* 1987; 84(23):8628-32.

[6] The pharmacological and physiological profiles of amylin are diverse, with nearly 60 different reported neuroendocrine actions on body systems. *See* Young A, Moore C, Herich J, Beaumont K. Chapter 9: Neuroendocrine actions of amylin. Poyner D, Marshall I, Brain S, Editor. *Calcitonin Gene-Related Peptide (CGRP)*. Austin, Texas: R.G. Landes, 1999: 91-102.

emptying, and obesity," *Lancet* 1975; 2:905-6. This is only the beginning, however. The PTO has not considered that, while some studies have reported differences in gastric emptying between obese and non-obese subjects,[7] others have not.[8]

A number of studies after 1975 compared gastric emptying of obese and nonobese subjects. In 1976 and 1983, respectively, accelerated transit through the proximal small intestine (Johansson C. and Ekelund K., "Relation between body weight and the gastric and intestinal handling of an oral caloric load," *Gut* 1976; 17:456-62) and gastric emptying of solids (Wright R.A., *et al.*, "Gastric emptying and obesity," *supra* note 9) were reported in the obese.

Later studies from 1983-1989, however, described delayed gastric emptying of solids and/or liquids in obese subjects. Horowitz M., *et al.*, "Effect of increasing the caloric/osmotic content of the liquid components of a mixed solid and liquid meal on gastric emptying in obese subjects," *supra* note 9;[9] Horowitz M., *et al.*, "Abnormalities of gastric emptying in obese subjects," *supra* note 9; Maddox A., *et al.*, "Gastric and oesophageal emptying in obesity," *supra* note 9. In addition, delays in orocecal

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[7] Wright R.A., *et al.*, "Gastric emptying an obesity," *Gastroenterology* 1983:84:747-51; Horowitz M., *et al.*, "Effect of increasing the caloric/osmotic content of the liquid components of a mixed solid and liquid meal on gastric emptying in obese subjects," *Hum. Nutr. Clin. Nutr.* 1986; 40C:51-6; Horowitz M., *et al.*, "Abnormalities of gastric emptying in obese subjects," *Int. J. Obes.* 1983; 7:415-21; Maddox A., *et al.*, "Gastric and oesophageal emptying in obesity," *Scand. J. Gastroenterol.* 1989; 24:593-8.

[8] Sasaki H., *et al.*, "Hyperinsulinemia in obesity: Lack of relation to gastric emptying of glucose solution or to plasma somatostatin levels," *Metabolism* 1983; 32:701-5.; Swaminathan R., *et al.*, "Thermic effect of feeding carbohydrate, fat, protein and mixed meal in lean and obese subjects," *Am. J. Clin. Nutr.* 1985; 42:177-81; Sasaki H., *et al.*, "Gastric function and obesity: Gastric emptying, gastric acid secretion, and plasma pepsinogen," *Int. J. Obes.* 1985; 8:183-90; Vezina W.C., *et al.*, "Increased volume and decreased emptying of the gallbladder in large (morbidity obese, tall normal, and muscular normal) people," *Gastroenterology* 1990; 98:1000-7; Zahorska-Markiewicz B, Jonderko K, *et al.*, "Gastric emptying in obesity," *Hum. Nutr. Clin. Nutr.* 1986; 40C:309-13.

[9] "This study has demonstrated a moderate delay in gastric emptying of solid food and a tendency for delayed liquid emptying in obese patients compared to control subjects for both test meals, consistent with the results of our previous study (Horowitz *et al.*, 1983*a*)" (emphases added).

transit have been observed in obese patients. Basilisco G., *et al.*, "Orocecal transit delay in obese patients," *Dig. Dis. Sci.* 1989; 34:509-12.

Five other studies from 1983-1990 showed no differences in gastric emptying. Sasaki H., *et al.*, "Hyperinsulinemia in obesity: Lack of relation to gastric emptying of glucose solution or to plasma somatostatin levels," *supra* note 10; Swaminathan R., *et al.*, "Thermic effect of feeding carbohydrate, fat, protein and mixed meal in lean and obese subjects," *supra* note 10; Sasaki H., *et al.*, "Gastric function and obesity: Gastric emptying, gastric acid secretion, and plasma pepsinogen," *supra* note 10; *supra* note 10; Zahorska-Markiewicz B, Jonderko K, *et al.*, "Gastric emptying in obesity," *supra* note 10; Vezina W.C., *et al.*, "Increased volume and decreased emptying of the gallbladder in large (morbidity obese, tall normal, and muscular normal) people."

The following conclusions regarding obesity and gastric emptying from articles published from 1989 to 1993 are highlighted:

- "Our study has, however, confirmed that as a group obese subjects have a moderate delay in gastric emptying of digestible solid and caloric liquid meals. These findings suggest that disordered gastric emptying is not a major factor in the pathogenesis of obesity." A. Maddox *et al.*, "Gastric and Oesophageal Emptying in Obesity," *supra* note 9 (emphasis added; footnotes omitted);

- "The gastric emptying, expressed as the half-emptying time ($T_{½}$) and mean transit time (MTT_{90}), in 31 obese and 21 control women was studied using a radionuclide technique. No correlation between body weight and body surface area and gastric emptying rates could be found. $T_{½}$ was slightly shorter and MTT_{90} faster in the obese women than in the controls. There is little chance that a subtle difference in gastric emptying is of any importance in the pathogenesis of obesity. B. Zahorska-Markiewicz *et al.*, "Gastric Emptying in Obesity," *supra* note 10.

- "There was no correlation between weight or body surface area and rate of solid or liquid gastric emptying. It is concluded that no relevant disturbance in gastric

> emptying is related to the pathogenesis of obesity." B. Glasbrenner *et al.*, "Gastric Emptying of Solids and Liquids in Obesity," *Clinical Investigator* (1993) 71:542-546 (emphasis added);

The indications of no disordered gastric emptying in the obese would not suggest the use of agents to alter it. The indications by still other groups of researchers who noted – not an increase in the rate of gastric emptying in obesity – but a delay, plainly teach away from the use of therapeutic agents to slow gastric emptying. The art would not counsel the development or use of agents to further delay gastric emptying for treatment of a disease where it is already abnormally delayed.

In an effort to reconcile the conflicting literature on this subject, researchers in 1993 performed both gastric emptying and gastroduodenal motility studies in morbidly obese and nonobese control subjects. They hypothesized that acute weight reduction may increase gastric emptying, thus altering satiety to promote restoration of their weight. Hutson R.H. and Wald A., "Obesity and Weight Reduction Do Not Influence Gastric Emptying and Antral Motility," *Am. J. Gastroenterology* 1993; 88:1405-09. However, the study was reported to strongly suggest that gastric emptying and antral motility are similar in obese and nonobese subjects, and that acute weight reduction does not affect gastric emptying. Hudson and Wald concluded that:

> (1) "acute weight reduction did not alter gastric emptying in our subjects, and would appear to play no potential role in promoting restoration of weight, as we had hypothesized" (emphasis added);
>
> (2) "significant alterations in gastric emptying or antral motility do not appear to occur in obese individuals; neither do they appear to change following acute weight reduction" (emphasis added); and,
>
> (3) "neither gastric emptying nor antral motility appear to be abnormal in morbidly obese subjects; neither does gastric emptying appear to be affected by substantial acute weight reduction" (emphases added).

They added, therefore, that, "Additional research is required to clarify further the mechanisms involved in the development and maintenance of obesity."

The results of studies of the effect of body weight on gastric emptying of solids and liquids were thus inconsistent. Accelerated,[10] delayed,[11] and unchanged gastric emptying,[12] have all been reported. Whether changes in gastric emptying are a primary cause of obesity is unknown. *See, e.g.*, Chiloiro M., *et al.*, "Gastric emptying in normal weight and obese children – an ultrasound study," *International Journal of Obesity* (1999) 23:1303-1306 (page 1303: "It is not yet known whether disturbances in gastric motility are involved in the complex pathogenesis of [obesity]"; page 1305: "Our data show that there are no differences in fasting antral area and gastric emptying curves between normal weight and obese children").

It has been reported that approximately 280,000 adult deaths in the United States each year are attributed to obesity, Allison DB, *et al.*, "Annual deaths attributable to obesity in the United States," *JAMA*, 1999;282:1530-1538, and that obesity has reached "epidemic proportions." The grave economics of the disease have also been the focus of attention. According to one 2002 article:

> The total costs associated with obesity and overweight are staggering: $99.2 billion, with $51.6 billion – or 5.7% of total health care expenditures in the United States – in direct health care costs for preventive, diagnostic, and treatment services, and $47.6 billion in indirect costs, such as time lost from work because of illness or disability and future earnings lost because of premature death.

[10] *E.g.*, Wright RA, *et al.*, "Gastric emptying and obesity," *supra* note 9.

[11] *E.g.*, Horowitz M, *et al.*, "Abnormalities of gastric emptying in obese patients," *supra* note 9.

[12] Sasaki H, *et al.*, "Gastric function and obesity: gastric emptying, gastric acid secretion, and plasma pepsinogen," *supra* note 10.

Blackburn, G.L., "Managing Obesity In America: An Overview," *Advanced Studies in Medicine* Vol. 2, No. 2, pages 40-49 (January 2002). Thus, if the treatment of obesity were a simple matter of identifying and marketing any agent that might slow gastric emptying as a treatment for obesity – as hypothesized by the PTO – it surely would have been done by now. On the contrary, however, the Minnesota Medical Association recently reported that, "Gastric emptying is useful in treating diabetics, but researchers are uncertain whether it will produce weight loss" (citing Cooper SJ, et al., "CCK antagonists and CCK-monoamine inter-actions in the control of satiety," *Am J Clin Nutr* 1992;55:291S-5S). *Minnesota Medicine* (November 2000/Volume 83) (emphasis added).

In sum, just as there is no agreement on the causes of obesity, and their impact on weight, there is no agreement on the effect of gastric emptying in obesity. Various articles report that the role of gastric emptying in obesity was uncertain and controversial both at the time of filing of the instant application, as well as before and after. Applicants also ask that the PTO take notice of the admonishment by the court in *In re Graf*, 343 F.2d 774, 777, 145 USPQ 197, 199 (CCPA 1965), that "obviousness is not to be determined on the basis of purpose alone." The *Graf* court held, "While a selection of certain facts in this case tend to a conclusion of non-obviousness and others taken alone may show obviousness, the conclusion required under section 103 must be grounded on a weighing of all the facts" (emphasis by the court). *Id.* The rejections made by the PTO in this case, however, are based on documents representing only a tiny fraction of what was known and understood in the art at the time regarding obesity, the multifactorial nature of the condition, treatment of obesity, and the many attempts to treat or try to treat obesity in view of its epidemic status in the United States. Similarly, only a small portion of the picture surrounding amylin is presented in the Office Action.

The PTO Did Not Correctly Discuss the State of the Amylin Art

Notably missing from the PTO analysis, among other things, is a description of the state of understanding of amylin and its functions at the time the subject application was filed. In addition to the various patents discussed above, as well as the 1997 Lutz *et al.* article, Applicants refer the PTO, for example, to a 1995 review article published by the scientist who discovered the amylin hormone, Dr. Garth Cooper.[13] In Cooper, "A reappraisal of current hypotheses concerning the possible roles of amylin in physiology, pathology and therapeutics," *Clin Sci* 88:7, 1995, Dr. Cooper catalogued the then-existing knowledge concerning amylin.[14] Specifically, he noted that obesity was believed to be characterized by an abnormal excess of amylin, stating that:

> Pathologically increased circulating amylin is regarded as a disease mechanism underlying islet dysfunction and insulin resistance in a variety of disease states, including obesity, essential hypertension and early NIDDM [*id.* at 8; emphasis added].[15]

[13] U.S. Pat. No. 5,367,052, issued November 22, 1994, to Cooper and Willis for "Amylin Peptides."

[14] *See, e.g.*, the discussion at page 8 (footnotes omitted):

> In skeletal muscle, there is evidence that amylin (i) decreases the rate of glucose incorporation into glycogen, (ii) decreases insulin-stimulated glucose transport, (iii) lowers glycogen content, (iv) stimulates glycogen phosphorylase, and (v) decreases the activity of glycogen synthase. *In vivo*, amylin (vi) stimulates release of lactate from peripheral tissues, (vii) decreases peripheral glucose clearance, and (viii) increases endogenous glucose production, the latter almost certainly through (ix) accelerated hepatic gluconeogenesis. Both peptides function as (v) dose-dependent antagonists of insulin in skeletal muscle, evoke states of (xi) experimental insulin resistant in living animals, and (xii) inhibit glucose-stimulated insulin secretion (reviewed below).

[15] Dr. Cooper wrote:

> The field has recently produced several novel hypotheses concerning the physiological regulation of fuel metabolism, and the mechanisms and therapeutics of diabetes and other conditions associated with insulin resistance. In the first of these, amylin and CGRP are considered to be novel physiological regulators of fuel metabolism. In the second, pathologically increased circulating amylin is regarded as a disease mechanism underlying islet dysfunction and insulin resistance in a variety of disease states, including obesity, essential hypertension and early NIDDM. Consistent with this idea, pancreatic mRNA, amylin secretion rates and circulating amylin concentrations are markedly elevated in appropriate rodent models. This concept led to the proposal that amylin blockers could serve as novel therapeutic agents for insulin resistance. In the third hypothesis, amylin deficiency in insulin-dependent diabetes (IDDM) is proposed as

This review of the art teaches away from any therapy based on administering amylin or agonists of amylin. Indeed, noting that insulin resistance "is thought to be the earliest metabolic abnormality detectable in individuals destined to subsequently develop . . . obesity" (*id.* at 9), Dr. Cooper discussed increased amylin as "a direct mechanism linking insulin resistance with obesity" (*id.* at 10). He suggested the use of antagonists of amylin to treat obesity, writing:

> This concept led to the proposal that amylin blockers [*i.e.*, antagonists] could serve as novel therapeutic agents for insulin resistance [*id.* at 8].

In addition to the '014 and '841 amylin antagonist/anti-obesity patents discussed above, other issued United States patents also reference the treatment of obesity with amylin antagonists.

- U.S. Patent No. 6,451,783, issued on September 17, 2002 to Hadcock, *et al.* on application filed January 16, 2001 for "Treatments for obesity and methods for identifying compounds useful for treating obesity," refers to amylin antagonists as "antiobesity agents."

- U.S. Patent No. 6,399,601, issued on June 4, 2002 to Du Bois on application filed September 27, 2000 for "Bicyclic pyrrolyl amides as glycogen phosphorylase inhibitors," refers to amylin antagonists as "antiobesity agents."

- U.S. Patent No. 6,369,075 issued April 9, 2002 to Ruggeri, *et al.* on application filed November 9, 2000 for "7[4'-trifluoromethyl-biphenyl-2-carbonyl)amino]-

a mechanism promoting excessive insulin sensitivity and hypoglycaemia in the insulin-treated disease. This latter hypothesis leads to the concept of co-replacement of amylin with insulin in IDDM, the aim being to minimize the occurrence of hyglycaemia and to improve glycaemic control.

quinoline-3-carboxylic acid amides, and method of inhibiting the secretion of apolipoprotein B," refers to amylin antagonists as "antiobesity agents."

- U.S. Patent No. 5,625,032 issued April 29, 1997 to Gaeta, *et al.* on application filed July 21, 1993 for "Selective amylin antagonist peptides and uses therefor," teaches the use of amylin antagonists for the treatment of obesity.

- U.S. Patent No. 5,580,953 issued December 3, 1996 Albrecht, *et al.* on application filed November 19, 1991 for "Amylin antagonist peptides and uses therefor," teaches the use of amylin antagonists for the treatment of obesity.

- U.S. Patent No. 5,260,275 issued November 9, 1993 to Cooper, *et al.* on application filed August 14, 1990 for "Hypoglycemics," states: "Excessive production of amylin from the pancreas is also responsible for the insulin resistance seen in patients with impaired glucose tolerance, obesity, and early type 2 diabetes mellitus. *See* Cooper *et al.*, *Proc. Natl. Acad. Sci. USA*, 1988; Leighton & Cooper, *Nature*, 1988; Cooper *et al.*, *Biochem. Biophys. Acta*, 1989; Molina et al., *Diabetes*, 1990" [emphasis added].

The information is these documents should be considered in the PTO analysis of the patentability of the inventions described and claimed in the instant case.

Applicants turn now to the specific objections and rejections that were set out in the Office Action mailed May 30, 2002.

Objections to the Specification

The PTO objected to Applicants' incorporation of WPI Acc. No. 93-182488/22 by reference on page 14, lines 10 and 26, of the present specification. In making this objection, the Examiner alleges that "the contents of the foreign application appear to be essential material for the instant invention." Applicants respectfully disagree, but have reworded the specification to include material incorporated by reference in order to expedite prosecution. Attached to this Response is an Affidavit, executed by Applicants' Representative, stating that the new paragraphs consist solely of material incorporated by reference. No new matter is included in these paragraphs. Thus, withdrawal of this objection is respectfully requested.

Second, the PTO objects to the specification's recitation of the abbreviations "ED_{50}," "$ED_{50}S$," and "IC_{50}." In making this objection, the Examiner asserts that it "is unclear what do these terms stand for or mean." The abbreviations "ED_{50}" (effective concentration 50%) and "IC_{50}" (inhibitory concentration 50%) are well known in the art to refer, respectively, to the amount of material required to produce a specified effect in 50% of individuals (ED_{50}) and, in determinations of receptor binding affinity of a ligand using a competitive binding curve, the concentration required for 50% inhibition (IC_{50}). *See, e.g.*, Gilman *et al.*, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, page 45 (7th ed. 1985) and *The Dictionary of Cell Biology* (1989). "$ED_{50}S$" recited on page 39 is merely the plural form of "ED_{50}." Applicants respectfully request that this objection be reconsidered and withdrawn.

Third, the PTO objects to the format in which certain trademarks are recited in the specification. The Examiner cites MPEP §608.01(v) in asserting that each letter of the trademark must be capitalized.

Applicants have reformatted the way that trademarks are referenced throughout the specification in order to expedite prosecution

35 U.S.C. §102

The First Rejection

Claims 1-6 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Thompson *et al.* (Diabetes, 46:Suppl. 1, page 30A, 0116, (1997)). This abstract was published by employees of Amylin Pharmaceuticals, Inc., assignee of the instant application, and the Examiner will note that the last named author is applicant Dr. Orville Kolterman. As noted above, the parent application to the instant case was filed on June 6, 1997. Applicants made their invention well prior to the May 2, 1997 date indicated for the Thompson *et al.* (May 1997) Abstract, and inventor Dr. Kolterman is a co-author. Included herewith is a Declaration under 37 CFR 1.131 antedating this references, and all others used as a basis for rejection under 35 U.S.C. §102(a). *See also In re Katz*, 215 USPQ 14 (CCPA 1982) and MPEP 715.01(c), and *In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957). One's own work is not prior art under §102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under §102(a). *See, e.g., In re Fout*, 213 USPQ 532 (CCPA 1982) (absent statutory bar, an applicant's own invention cannot be "prior art" to him); *In re Facius*, 161 USPQ 294, 302 (1969) ("one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar").

Thus, despite other bases for the removal of this rejection it is respectfully requested that that the rejection over Thompson *et al.* (May 2, 1997) be reconsidered and withdrawn as it does not meet the legal requirements for anticipation under Section 102(a).

The Second Rejection

Claims 1-3 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by MacDonald *et al.* (Diabetologia, 38:Suppl. 1:A118 (1995)) – MacDonald *et al.* being a document relating to a study of the infusion of pramlintide in eight men with type 1 diabetes (in whom glucose levels were maintained within 3mM of a pre-meal value) – "as evidenced by Robert *et al.* (PCT Publication No. WO91/16917)." The PTO states without explanation at page 8 of the Office Action that it "views inhibition of gastric emptying as an inherent amylin agonistic, body-weight reducing function of pramlintide." On page 8 of the Office Action, the PTO took the following further position:

> It is inherent that by significantly delaying gastric emptying in the treated patients, the pramlintide used in MacDonald's method necessarily induces weight-controlling or weight-reducing effects, and symptom-relieving effects, since it is well known in the art that that anti-gastric emptying agents also serve as weight reducing agents. For instance, Robert *et al.* demonstrated that that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss.

MacDonald *et al.* refers to the intravenous infusion of 125 micrograms of pramlintide to human subjects with insulin-using type 1 diabetes, and reports that gastric emptying was delayed such that "t50 values could not be calculated for solid or liquid meal components." On this basis, the Examiner alleges that treatment of obesity is "inherent" because "it is well known in the art that anti-gastric emptying agents also serve as weight-reducing agents," citing Robert *et al.*, which is asserted by the Examiner to demonstrate "that a gastric emptying-retarding compound also serves as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss." Although Robert *et al.* contains no such demonstration, with this duo of documents, citing *In re Samour*, 197 USPQ 1 (CCPA), the Examiner alleges that "[t]he teachings of MacDonald *et al.* anticipate the instant claims."

Initially, Applicants note that the MacDonald *et al.* Abstract also relates to clinical work of assignee Amylin Pharmaceuticals, Inc., the next to last named author being Dr. Chris Moyses, its employee at that time. Applicants also note that type 1 diabetes usually occurs in people who are thin or of normal weight, and patients with type 1 diabetes are typically thin, not obese. This person is of normal weight or thin when type 1 diabetes starts and often stays relatively trim through life. *See* American Diabetes Association, "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus," *Diabetes Care* 2001;23:S4-S19.

It is well settled that the burden of establishing a *prima facie* case of anticipation resides with the PTO. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984); *In re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967). In relying upon the theory of inherency, furthermore, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent feature or features necessarily flow from the teachings of the applied prior art. *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); *In re Oelrich and Divigard*, 666 F.2d 578, 212 USPQ 323 (CCPA 1981); *In re Wilding*, 535 F.2d 631, 190 USPQ 59 (CCPA 1976); *Hansgirg v. Kemmer*, 102 F.2d 212, 40 USPQ 665 (CCPA 1939). Applicants respectfully submit that the Examiner has not discharged this burden.

MacDonald *et al.* says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals. The study was carried out, according to MacDonald *et al.*, to assess whether delayed gastric emptying played a role in the ability of the amylin agonist pramlintide to reduce hyperglycemia (high blood sugar). MacDonald is limited to teaching <u>one</u> particular amount of

pramlintide (25 μg/hr) infused intravenously over only a 5 hour period. No further studies are described. No weight loss over this 5 hour period is described. MacDonald *et al.* reports that the infusion of pramlintide in this particular study resulted in a delayed gastric emptying, leading to the supposition that pramlintide "may be of value in regulating assimilation of ingested nutrients" in people with type 1 (*i.e.*, insulin-using) diabetes. MacDonald *et al.* fails to provide any working example revealing the process of the pending claims. MacDonald fails to teach or suggest any treatment for obesity, let alone a protocol for the administration of pramlintide to treat obesity.

Indeed, as noted above, it was and is well known that IDDM (or type 1) patients are typically thin, not obese. Thus, there is no basis for the assertion that treatment of obesity is "inherent" in the MacDonald *et al.* Abstract or that any of the listed claims is anticipated. It is the law that inherency "may not be established by probabilities or possibilities." *See, e.g., Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient," quoting *In re Oelrich and Divigard*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981)).

In making this 102 rejection, the Examiner cites *In re Samour* for the proposition that Robert *et al.* is relied upon "to show that every element of the claimed subject matter is disclosed by MacDonald et al." Thus, the Examiner appears to rely on *Samour* to establish that MacDonald (i) contains an enabling disclosure, or (ii) to show that a characteristic not disclosed in MacDonald is inherent (*see* MPEP 2131.01). Indeed, in order for a document to qualify as prior art the alleged reference must be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention. *See, e.g., PPG Indus., Inc. v. Guardian Indus.*

Corp., 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter" (emphases added)). *See also In re Paulsen*, 30 F.3d 1475, 1478, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (To be anticipating, a prior art reference must disclose "each and every limitation of the claimed invention [,] . . . must be enabling[,] and [must] describe . . . [the] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention."). MacDonald fails to provide such a teaching for the treatment of obesity. Furthermore, like MacDonald, Robert *et al.* does not provide an enabling description for the dosage or administrative of any amylin agonist that could be used for the treatment of obesity. Thus, the rejection for alleged anticipation on the basis of inherency is not saved by citation to the Robert *et al.* patent application.

Robert *et al.*, published on November 14, 1991, does not have anything to do with amylin or amylin agonists. Robert *et al.* discusses the proposed use of a cytokine, Interleukin-1, to cure or prevent gastric ulcers, and describes gastroprotection studies in which Interleukin-1 was given to experimental rats that were killed within 30, 60 or 120 minutes following administration. Robert *et al.* further alleges that Interleukin-1 treatment may be of use in "retarding emptying of gastric contents [*sic*]" in order to reduce "a patient's desire for food" which in turn, it is alleged, may be "helpful in weight loss programs." Page 2, lines 22-26. The only "patients" subjected to IL-1 in Robert *et al.* were rats. No determination was reported that these rats had a reduced desire for food. As described above, the experiments reportedly performed were strictly short term and there was no determination of any alleged weight loss in the rats. The conjecture in the Robert *et al.* application relating to obesity appears to be limited to the passage at page 5, lines 1-3, where it is asserted that, "By reducing gastric motility, food will remain in the stomach longer and thereby, reduce the appetite of the patient."

In the only experiment allegedly relating to gastric emptying, rats were killed 4 hours after Interleukin-1 administration, which is clearly an insufficient time to evaluate weight, treatment of "obesity," or alleged appetite reduction. Indeed, Robert *et al.* state that "it is equally plausible that the anorexia of fever is related to delayed gastric emptying caused by IL-1," and only speculate that "appetite is likely to be lost when the stomach remains filled." Page 8, lines 30-34 (emphases added). In the Robert *et al.* "Example 2," furthermore (which is wholly prophetic, and not a working example), the authors theorize only that Interleukin-1 "is presumed to act either by acting on appetite centers in the central nervous system, or by retarding the emptying of food from the stomach." Page 9, line 36 to page 10, line 2 (emphases added). Indeed, it is reported that IL-1 might exert effects through entirely different mechanisms. IL-1 is postulated to act directly on the hypothalamus, and to increase the synthesis of tryptophan. Laviano, A. *et al.*, "Peripherally injected IL-1 induces anorexia and increases brain tryptophan concentrations," *Adv. Exp. Med. Biol.* 467:105-08 (1999).

Contrary to the statement made by the PTO at page 8 of the May 30, 2002 Office Action, Robert *et al.* thus cannot be said to have "demonstrated" that "a gastric emptying-retarding compound also serves as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss", and its citation under the authority of *In re Samour* cannot complete the rejection of pending claims 1-3 under Section 102.

Applicant respectfully submits that the PTO has failed to provide the required basis in fact or technical reasoning to support a determination that a treatment for obesity necessarily flows from the short term delay in gastric emptying purportedly demonstrated in MacDonald. Applicants further

submit that the PTO has failed to meet its burden of establishing a *prima facie* case of anticipation. Accordingly, Applicants respectfully request that the rejection of claims 1-3 under 35 U.S.C. §102(b) as allegedly anticipated by MacDonald *et al.*, "as evidenced by Robert *et al.*," be reconsidered and withdrawn.

The Third Rejection

Claims 1-6 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by by Thompson *et al.* (Diabetes, 46:632-6 (April 1997)), "as evidenced by Guthrie *et al.*" (U.S. Patent No. 4,443,619). The Thompson *et al.* paper also relates to clinical work of assignee Amylin Pharmaceuticals, Inc., and all listed authors were or are employees of Amylin Pharmaceuticals.

The Examiner asserts that Thompson *et al.* (April, 1997) teaches the subcutaneous administration of pramlintide to insulin-using type 1 diabetics at a dose of 30 or 100 μg QID or TID for four weeks, and relies upon the reported induction of "a dose-dependent anorexia and nausea in pramlintide-treated patients" and the asserted "modulation of gastric emptying" to allege that claims 1-6 are unpatentable for lack of novelty. The Examiner again relies on alleged inherency, alleging without any direct support that "the anorexic and gastric emptying-slowing effects of pramlintide . . . necessarily result in therapeutic weight loss" because "therapeutic agents with these effects have been successfully used in the art as anti-obesity agents in the treatment of obesity or weight gain," citing Guthrie *et al.* According to the Examiner, Guthrie *et al.* is alleged to teach "the treatment of obesity in mammals with the use of anorectic agents that delay gastric emptying."

As noted above, in order to establish inherency the Examiner is obliged to provide a technical basis to support the determination that the allegedly inherent feature or features necessarily flow from

the teachings of the applied prior art. The Examiner has again not discharged that burden. Thompson *et al.* says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals, stating only in a section entitled "Safety Data" regarding the treatment of normally thin type 1 diabetics, that "the most frequent adverse events involved upper gastrointestinal symptoms (nausea, anorexia, and dyspepsia) and occurred more frequently in patients in the pramlintide groups than in patients in the placebo group." Page 635, col. 1 (emphasis added). The paper acknowledges that "anorexia" was reported in only 2.4% of the patients who received 30 μg pramlintide and in only 9.5% of the patients who received 30 μg pramlintide. The paper further reports that, "No patients on pramlintide who reported anorexia in the 1st week reported this adverse event in the 2nd week of administration." *Id.* (emphasis added). As a matter of law this cannot establish "inherency" of the claimed methods. Inherency can only be demonstrated by a showing that the methods are the inherent, inevitable result of the practice of another method. *See, e.g., In re Oelrich and Divigard*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 USPQ 665, 667 (1939) (same). Because anticipation by inherent disclosure is appropriate only when the alleged reference discloses prior art that must necessarily include the unstated limitation, *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (emphasis added), the Thompson *et al.* document cannot inherently anticipate the claims of the instant application.

The Examiner's citation of the 1984 patent to Guthrie *et al.*, which issued three years before the discovery of amylin, cannot make up for the inability to present the required showing of inevitability. Citing *In re Samour*, 197 USPQ 1 (CCPA 1978), the Examiner alleges that Guthrie *et al.* shows "the

treatment of obesity in mammals with the use of anorectic agents that delay gastric emptying." Guthrie *et al.* cannot complete the rejection, however, particularly in view of the fact that it was published prior to the discovery of both amylin and pramlintide. It is established that to serve as an anticipation when the reference is silent about an asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. That evidence, however, "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Finnigan Corp. v. ITC*, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999) (emphases added); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159, 47 USPQ2d 1829, 1834 (Fed. Cir. 1998). The Examiner has not established that both of these requirements are met. Additionally, although not necessary to establish that the rejection is properly withdrawn, Applicants note the Guthrie *et al.* patent shows that certain rats given the claimed compounds gained weight or did not reduce their food consumption. *See, e.g.*, "Example 6 [*sic*, 16]" showing that rats given a chlorocitric acid of the invention gained weight. Still other results indicate that the food intake of rats in certain experiments were also no different from control.

There is no inherent anticipation, and Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. §102(a) as allegedly "anticipated by Thompson *et al.* (Diabetes, 46:632-6 (April 1997)) as evidenced by Guthrie *et al.* (U.S. Patent No. 4,443,619)" be reconsidered and withdrawn.

As noted above, the parent application to the instant case was filed on June 6, 1997. Applicants made their invention well prior to the date indicated for Thompson *et al.* (April, 1997). Although unnecessary, as noted above, Applicants have filed a Declaration under 37 C.F.R. § 1.131, which is deemed sufficient to remove this article as an alleged reference as well.

The Fourth Rejection

Claims 1-6 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) in light of Flexner *et al.*, Ed., The Random House Dictionary, New York, p. 32 (1984). The Kolterman *et al.* paper also relates to clinical work of assignee Amylin Pharmaceuticals, Inc., and all listed authors were employees of Amylin Pharmaceuticals, including applicant Dr. Kolterman.

The Examiner asserts that Kolterman *et al.* (April, 1996) teaches the subcutaneous administration of pramlintide to insulin-using type 1 diabetics at a dose of 30, 100 or 300 μg TID for 14 days, and relies upon the reported induction of "anorexia, recurrent nausea and significant reduction in postprandial hyperglycemia" to assert that claims 1-6 and 11-15 are unpatentable for lack of novelty on the allegation that the method of Kolterman et al. "necessarily serves as a method of treating obesity." On page 17 of the Office Action, the Examiner relies once more on alleged inherency, and incorrectly asserts that treatment of obesity "is inherent from the teachings of Kolterman *et al.*"

The Examiner asserts that pramlintide induced "anorexia" and "recurrent nausea." On this basis, without further explanation and without any citation to the document relied upon, the Examiner concludes that the Kolterman *et al.* method regarding normally thin type 1 diabetics allegedly "necessarily causes abnormal lack of appetite, thereby decreasing if not inhibiting, the food intake, or the quantity or frequency of food intake, which in turn controls the body weight of the patients for cosmetic purposes or improves the bodily appearance of the patients administered with [*sic*] pramlintide." Contrary to the conclusions of the Examiner in her 2002 Office Action, Kolterman *et al.* concluded none of these things six years earlier in their 1996 publication. In an effort to complete the

rejection, however, the Examiner relies upon Flexner *et al.*, Ed., The Random House Dictionary, New York, p. 32 (1984), to assert that anorexia is an "abnormal lack of appetite."

The Examiner has not discharged the burden of establishing that the allegedly inherent feature or features necessarily flow from the teachings of the alleged prior art. Kolterman *et al.* says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals – let alone, as hypothesized by the Examiner, improving "the bodily appearance" of individuals given pramlintide – stating only in the section entitled "Adverse Events" that the "only significant side effects noted were gastrointestinal in origin and included primarily nausea with occasional emesis and complaints of anorexia." Page 497, col. 1 (emphasis added). The paper further states that, "None of these episodes were considered serious." The paper concludes with no reference to weight or obesity, but only with the statement that the observations from the study "will be extended in future studies to evaluate the extent to which amylin replacement can improve glucose control throughout the entire 24-h period." The PTO itself acknowledges at page 19 of the June 5, 2002 Office Action that Kolterman *et al.* (1996) is "silent about the body weight of the human subjects following pramlintide treatment."

As a matter of law this cannot establish "inherency" of the claimed methods of treating obesity, which can only be demonstrated by a showing that the methods are the inherent, inevitable result of the practice of another method. *See, e.g., In re Oelrich and Divigard*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (quoting Hansgirg v. Kemmer, 102 F.2d 212, 214, 40 USPQ 665, 667 (CCPA 1939)); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159, 47 USPQ2d 1829, 1834 (Fed. Cir. 1998) ("In order for a disclosure to be inherent .

. . the missing descriptive matter must necessarily be present in the . . . application's specification such that one skilled in the art would recognize such a disclosure."); *Ex parte Levy*, 17 USPQ2d 1461, 1464 ((BdPatApp&Int 1990) ("In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.").

Thus, Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. §102(b) as allegedly anticipated by Kolterman *et al.* (1996) in light of Flexner *et al.* be reconsidered and withdrawn.

The Fifth Rejection

Claims 1-6 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Kolterman *et al.* (PCT Publication No. WO95/07098). The Kolterman *et al.* '098 application also relates to work within assignee Amylin Pharmaceuticals, Inc., and all listed inventors were or are employees of Amylin Pharmaceuticals, including applicant Dr. Kolterman. This application was published on March 16, 1995. U.S. patents claiming priority from the U.S. application from which the Kolterman '098 patent claims priority have now issued as U.S. Patent Nos. 5,795,861 and 6,114,304.

The Examiner asserts that the Kolterman *et al.* '098 application teaches a method comprising the administration of an amylin or an amylin agonist such as pramlintide, and that it describes the results of a study in which pramlintide was administered to insulin-using type 1 diabetics at a dose of 30, 100 or 300 μg TID for 14 days. The Examiner notes that the method results in a reduction in postprandial glucose levels and delayed gastric emptying. As in previous rejections, the Examiner relies on alleged inherency and states that the "method serves necessarily as a method of treating obesity or controlling

body weight" and "inherently and necessarily brings about the same therapeutic effects brought about by the Applicants' methods, *i.e.*, controlling weight for cosmetic purposes, or controlling body weight to improve bodily appearance in humans."

With regard to gastric emptying, however, the Kolterman et al. '098 application describes the use of agents that delay gastric emptying, for example, as "diagnostic aids in gastro-intestinal radiologic examinations" (page 19) and for the "treatment of insulin-induced hypolyceamia" (page 19-20). The application does not mention the use of agents to delay gastric emptying in the treatment of obesity or for weight control. The application also describes the use of amylins and amylin agonists for treatment of postprandial hyperglycemia (*i.e.*, high post-meal blood sugar; *e.g.*, page 21), for subjects undergoing a gastrointestinal diagnostic procedure (*e.g.*, page 23), and for treatment of subjects suffering from a gastrointestinal disorder (*e.g.*, page 23), post-prandial dumping syndrome (*e.g.*, page 23), or ingestion of a toxin (*e.g.*, page 24).

Applicants submit again that the Examiner has not discharged the burden of establishing that the allegedly inherent feature or features necessarily flow from the teachings of the Kolterman *et al.* '098 application. The Kolterman *et al.* '098 application says nothing about body weight, weight reduction, weight control, treatment of obesity, or the treatment of obese individuals. It also does not refer to the use of amylins or amylin agonists for "controlling weight for cosmetic purposes, or controlling body weight to improve bodily appearance," as submitted by the Examiner.

As a matter of law the Kolterman '098 application cannot establish "inherency" of the claimed methods of treating obesity, which can only be demonstrated by a showing that the methods are the inherent, inevitable result of the practice of another method. *See, e.g., In re Oelrich and Divigard*, 666

F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); *Hansgirg v. Kemmer*, 102 F.2d 212, 214, 40 USPQ 665, 667 (1939) (same). Applicants therefore respectfully request that the rejection of claims 1-6 under 35 U.S.C. §102(b) as allegedly anticipated by the Kolterman *et al.* '098 application be reconsidered and withdrawn.

The 35 U.S.C. §103(a) Rejections

A claimed invention is unpatentable as obvious only "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. Section 103(a) (1994). Obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the ordinary artisan, and objective considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). To establish a *prima facie* case of obviousness based on a combination of the content of various alleged references, there must be some objective teaching, suggestion or motivation in the prior art to make the specific combination. *In re Raynes*, 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). It has been held, furthermore, as noted above, that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine any alleged prior art references. *In re Gorman*, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). As discussed in *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985), it is the alleged prior art itself, and not the applicant's

achievement, that must establish the alleged obviousness of the combination. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher.").

The teachings of the alleged references, their relatedness to the field of the applicant's endeavor, and the knowledge of persons of ordinary skill in the field of the invention, are all relevant considerations. *See In re Oetiker*, 977 F.2d at 1447, 24 USPQ2d at 1445-46; *In re Gorman*, 933 F.2d at 986-87, 18 USPQ2d at 1888; *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). Thus, there is no suggestion that would support a conclusion of obviousness within the meaning of 35 USC 103 if an alleged reference teaches away from the invention, or from its combination with another source. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant . . . [or] if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

While in hindsight, looking at Applicants' invention, it apparently seems logical to the PTO to try an amylin or an amylin agonist for weight reduction or treatment of obesity, neither the amylin art nor the obesity art suggested such an approach or indicated that this approach, if tried, would likely succeed. Furthermore, while the art does not teach this approach, it is in any event the law that "obvious

to try" does not constitute obviousness. The Federal Circuit recently explained in *In re Eli Lilly & Co.*, 902 F.2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990), that:

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued.

According to the court, an invention is "obvious to try" where the alleged prior art gives "either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

In re O'Farrell also defines obvious-to-try as when alleged prior art gives "only general guidance as to the particular form of the claimed invention or how to achieve it." The Federal Circuit has held, however, that "A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). *See also In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1521, 1532 (Fed. Cir. 1988) (rejecting "obvious to try" standard); *In re Geiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987) (rejecting "obvious to try" as standard for determining obviousness); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1380, 231 USPQ 81, 91 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed. Cir. 1984) ("obvious to try" is improper consideration in adjudicating obviousness issue).

Moreover, the alleged teachings of the documents cited by the PTO must be weighed alongside the teachings of the art as a whole, including those documents discussed above and many others, which,

as explained, teach away from the use of amylin and amylin agonists as useful for weight reduction or the treatment of obesity.

The First Rejection

The rejection of claims 5-6 under 35 U.S.C. §103(a) over Arnelo I (Arnelo *et al.*, *Am. J. Physiol.*, 271(6):R1654-R1659 (1996)) or Arnelo II (Arnelo *et al.*, *Scand. J. Gastroenterol.*, 31:83-89 (1996)) as applied to claims 4 and 1, and further in view of Bennett *et al.*, U.S. Patent No. 5,955,443, was maintained in the May 30, 2002 Office Action. The PTO stated that the previous rejection, which was "maintained in paragraph of the Office Action mailed 12/18/01 (paper no. 28), is maintained for reasons set forth therein." This rejection is respectfully traversed.

Arnelo I does not teach or suggest treating obesity in human subjects. This is not surprising given that Arnelo I does not report weight loss in the experimental study performed on rats and described therein, and that their work allegedly only provided some "indirect evidence" of a potential "role in the physiological and/or pathophysiological control of food intake" (page R1658). The authors also note the lack of any connection between gastric emptying and food intake (page R1658). Indeed, Figure 4 of Arnelo I shows that every single animal in the eight day infusion study in fact gained weight – the gains ranging from about 5% to 20% total body weight. Applicants also refer the Examiner to the previously mentioned 1997 article by Lutz *et al.*, "Evidence for a physiological role of central calcitonin gene-related peptide (CGRP) receptors in the control of food intake in rats," *Neuroscience Letters* **230**:159-162 (1997). In this 1997 paper, Lutz *et al.* summarized art regarding amylin and food intake. Referring to the findings in fourteen articles spanning 1991 to 1996 – including the Arnelo I document cited by the PTO – the authors stated that "no clear evidence has been brought forward so far

establishing endogenous amylin or CGRP as endogenous satiety peptides" (emphasis added). Indeed, Arnelo I itself states that a "role for endogenous [amylin] in the physiological control of feeding behavior remains to be established" (page R1657). This constitutes objective evidence that those in the art did not share the analysis or conviction of the PTO regarding the alleged teachings of Arnelo I.

Arnelo II also does not teach or suggest treating obesity in human subjects. In contrast to the present invention, Arnelo II reported: "Bolus injection or infusion of human IAPP [which the authors call "amylin"] did not inhibit food intake at any dose" (page 85, last paragraph). With respect to injection or infusion of rat IAPP, Arnelo II reported that any feeding suppression effects therefrom had vanished by twenty-four hours when rat IAPP was administered at doses of 5 and 10 nmol/kg (page 85, last paragraph). Although the authors stated that they found an "effect on body weight during chronic infusion," Figure 4 on page 87 shows that the results obtained in the study group were not statistically significant (as opposed to those of the control group, which were reported to be significant at two time points). The authors also describe a "reduced effect with time" (page 88), and further admit that the "anorectic effect" allegedly described may be caused by "a non-specific effect such as malaise" (page 87). Clearly these results are not consistent with, and do not suggest (as confirmed by the above-referenced 1997 Lutz *et al.* paper) a treatment for obesity. The statement in the paragraph bridging pages 9 and 10 of the instant application referred to by the Examiner is plainly not inconsistent with this conclusion. It is well-understood that transient loss of appetite may be caused by nausea.

The citation of U.S. Patent No. 5,995,443, issued to Bennett *et al.* for "Antisense Modulation of PECAM-1" cannot complete the rejection. It relates to "thrombin inhibition" and has nothing whatever to do with amylin, amylin agonists, methods of weight control, or the treatment of obesity. The

Examiner may not properly rely on this document establish, as was suggested at page 10 of the October 18, 2001 Office Action in this case, "that the determination of effective doses of a pharmaceutical compound and the optimal frequency of its administration to a human subject based on the age, sex, weight, clinical condition and extent of a clinical condition in a human subject" are "within the realm of routine experimentation." This is both speculative and irrelevant to the specific invention of the instant application. Indeed, the Bennett *et al.* patent sets out specific doses and dose ranges for the alleged "compounds of the invention" – ranging "from 0.01 [micrograms] to 100 [grams] per kg of body weight, once or more daily, to once every 20 years." The administration amounts for such "thrombin inhibition" compounds in a typical 70 kilogram human thus range from 7 micrograms to 7000 grams "once or more daily, to once every 20 years." These doses and dose frequencies are vastly different from those set out for amylin and amylin agonists in the present application and in claims 5 and 6.

As set forth above, claim 5 defines the administration of an amylin or an amylin agonist from 1 to 4 times per day for the treatment of obesity. Claim 6 (which depends from claim 5) defines the administration of an amylin or an amylin agonist in an amount from about 30μg per dose to about 300μg per dose. In addition to the failure of these documents to teach or suggest treatment of obesity with of a composition comprising an anti-obesity agent consisting of an amylin or an amylin agonist, these amounts and the frequencies of administration are not suggested or taught by any of Arnelo I, Arnelo II, or Bennett *et al.*, and Applicants respectfully request that the rejection of claims 5 and 6 as allegedly obvious within the meaning of 35 U.S.C. §103(a) over Arnelo I or Arnelo, and further in view of the Bennett *et al.*, '443 patent, be reconsidered and withdrawn.

The Second Rejection

The rejection of claims 1-6 under 35 U.S.C. §103(a) as allegedly unpatentable over Kolterman *et al.* (WO 96/40,220) in view of Meglasson (U.S. Patent No. 5,134,164) was also maintained. This rejection is respectfully traversed.

Kolterman *et al.* (WO 96/40,220), entitled "Treatment of type II diabetes mellitus with amylin agonists," relates to methods of lowering blood sugar in patients with type 2 diabetes mellitus, who do not use insulin, by administration of an amylin agonist thereto. It states that "non-insulin- taking Type II diabetic patients may be treated by the administration of an amylin agonist in order to lower their blood glucose concentrations," one such agonist being ^{25,28,29}Pro-h-amylin. Kolterman *et al.* (WO 96/40,220) does not refer to weight loss or treatment of obesity.

According to the Examiner, however, it would have been obvious to use a compound that reduces hyperglycemia in type 2 diabetic patients, "as taught by Kolterman *et al.*," as a "method of reducing hyperglycemia for treating obesity to produce the instant invention" because Meglasson allegedly teaches that "any compound" useful for treating hyperglycemia "could also be used to treat or prevent obesity." December 18, 2001 Office Action at pages 11-12.

The Examiner cites the 1992 Meglasson patent for the proposition that it "explicitly" discloses "that hyperglycemia also occurs in obesity as it does in non-insulin dependent diabetes mellitus, also known as NIDDM or type II diabetes, and that a compound that is useful in the treatment of hyperglycemia 'could also be used to treat or prevent NIDDM' and 'obesity'." May 30, 2002 Office Action, page 11. Meglasson says no such thing.

What Meglasson does allege is that:

- "There are several metabolic disorders of human and animal metabolism, *e.g.*, hyperglycemia, impaired glucose tolerance, hyperinsulinemia and insulin insensitivity, hyperamylinemia, excess adiposity, and hyperlipidemia" (emphasis added);

- "Some or all of the above disorders may occur in the following disease states: non-insulin dependent diabetes mellitus (NIDDM), obesity, hypertension and atherosclerosis" (emphasis added); and,

- "Therefore, a compound that is useful in the treatment of hyperglycemia, impaired glucose tolerance, hyperinsulinemia, insulin insensitivity, hyperamylinemia, excess adiposity or hyperlipidemia could also be used to treat or prevent NIDDM, obesity, hypertension or atherosclerosis" (emphases added).

According to Meglasson, that compound is 3-guanidinopropionic acid (3-GPA). To Applicants' knowledge, however, 3-GPA is neither approved for the treatment of obesity or diabetes, and is not now and never was in human clinical development for the treatment of either disease.

Applicants also point out that Meglasson expressly states that excess amylin is characteristic of obesity. Stating that "[h]yperamylinemia can be seen in NIDDM and obesity" (emphasis added), the patent asserts that "3-GPA ameliorates hyperamylinemia and therefore is beneficial in treating disease states in which plasma amylin concentration is increased." Thus, this document also teaches away from the invention and provides further objectively evidence of nonobviousness. One skilled in the art would not read this patent to teach giving an amylin or amylin agonist to an obese patient whose amylin levels are abnormally elevated as a result of their obesity. See Table IV and Table V of Meglasson which

report, respectively, that 3GPA lowered amylin levels and decreased weight following administration of 3-GPA.

Furthermore, as noted above, Dr. Kolterman is a named inventor on the both instant application and the WO 96/40,220 document cited by the Examiner (the latter being related to U.S. Patent No. 6,417,164 issued to Kolterman *et al.* on July 9, 2002 and U.S. Patent No. 6,143,718 issued to Kolterman *et al.* on November 7, 2000, both for "Treatment of type II diabetes mellitus with amylin agonists"). The parent application to the instant case was filed on June 6, 1997. One's own work is not prior art under §102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under §102(a). *See, e.g., In re Fout*, 213 USPQ 532 (CCPA 1982) (absent statutory bar, an applicant's own invention cannot be "prior art" to him); *In re Facius*, 161 USPQ 294, 302 (1969) ("one's own invention, whatever the form of disclosure to the public, may not be prior art against oneself, absent a statutory bar"). Thus, despite other bases for the removal of this rejection it is respectfully requested that the rejection over Kolterman *et al.* (WO 96/40,220) be reconsidered.

Applicants further respectfully request that the rejection of claims 1-6 under 35 U.S.C. §103(a) over Kolterman *et al.* (WO 96/40,220) and Meglasson in its entirety be reconsidered and withdrawn.

The Third Rejection

Claims 1-6 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) in view of Robert *et al.* (PCT Publication No. WO91/16917). Kolterman *et al.* (1996)) is discussed above with respect to the fourth rejection under Section 102 and Robert *et al.* was discussed above with regard to the second rejection under Section 102. This rejection is respectfully traversed.

The PTO acknowledges at page 14 of the instant Office Action that Kolterman *et al.* (1996) is "silent about the body weight of the human subjects following pramlintide treatment." Despite this silence, however, the Examiner asserts that "it is implicit from Kolterman's (1996) teaching that their method necessarily served as a method of treating obesity or inducing weight loss . . . in light of what is known in the art." The Examiner continues, alleging that:

> By significantly delaying/restoring gastric emptying in the treated patients, the pramlintide used in Kolterman's (1996) method necessarily induced weight-controlling or weight-reducing effects, since it is well known in the art that anti-gastric emptying agents also serve as weight-reducing agents.

Thus the Examiner relies on inherency for the rejection. However, the statements in Kolterman (1996) do not support inevitability, which is required to demonstrate inherency.

In acknowledgement of this lack of support, the Examiner cites Robert *et al.* As discussed above, however, this does not save the rejection. The Robert *et al.* patent application does not relate to amylin. It concerns the proposed use of Interleukin-1 to cure or prevent gastric ulcers and, allegedly, to prevent obesity by "retarding emptying of gastric contents [*sic*]" in order to reduce "a patient's desire for food" which is in turn alleged to be "helpful in weight loss programs." Page 2, lines 22-26. As noted above, Robert *et al.* asserts at page 5, lines 1-3, that, "By reducing gastric motility, food will remain in the stomach longer and thereby, reduce the appetite of the patient."

However, this was not demonstrated. The work allegedly undertaken and described in Robert *et al.* related primarily to gastroprotection and was based on rat studies in which Interleukin-1 was given to experimental rats who were killed within one half hour to two hours following administration, which is not sufficient time to evaluate weight. Similarly, in the only experiment allegedly relating to gastric emptying, rats were killed 4 hours after Interleukin-1 administration, which is also an insufficient time

to evaluate weight, treatment of "obesity," or alleged appetite reduction. Indeed, Robert *et al.* state that "it is equally plausible that the anorexia of fever is related to delayed gastric emptying caused by IL-1," and that "appetite is likely to be lost when the stomach remains filled." Page 8, lines 30-34 (emphases added). In the Robert *et al.* "Example 2," furthermore (a wholly prophetic example), the authors state only that Interleukin-1 "is presumed to act either by acting on appetite centers in the central nervous system, or by retarding the emptying of food from the stomach." Page 9, line 36 to page 10, line 2 (emphases added).

Robert *et al.* thus cannot be said to establish or demonstrate that "a gastric emptying-retarding compound also serves as an anti-obesity agent by retaining the food in the stomach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss," as alleged by the Examiner, and its citation cannot complete the rejection of pending claims 1-6 under Section 103. IL-1, furthermore, might exert effects through entirely different mechanisms. IL-1 is postulated to act directly on the hypothalamus, and to increase the synthesis of tryptophan. See Laviano, A. *et al.*, "Peripherally Injected IL-1 Induces Anorexia and Increases Brain Tryptophan Concentrations," *Adv. Exp. Med. Biol.* 467:105-08 (1999), where the authors conclude at page 107 that, "Thus, it is conceivable to reason that IL-1 may induce anorexia directly by acting on the serotonergic hypothalamic neurons, and indirectly by facilitating serotonergic activity, *i.e.*, enhancing brain [tryptophan] supply, the precursor of serotonin" (emphasis added).

The Examiner cites to no specific language in either the Kolterman *et al.* (1996) article or the Robert *et al.* application patent demonstrating a motivation to combine. The Examiner merely refers to the alleged "inherent teachings" of Kolterman *et al.* and the Robert *et al.* application concerning an

unrelated protein, Interleukin-1. This does not and cannot constitute meaningful evidence of inherency, *i.e.*, inevitability, and the pertinent inquiry under Section 103 has not been satisfied. As noted above, the Federal Circuit has emphasized that where an alleged reference that is silent about an asserted inherent characteristic, such a gap can only be filled with recourse to extrinsic evidence that "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749(Fed. Cir. 1991). This requirement, that a person of ordinary skill in the art must recognize that the missing descriptive matter is necessarily present in the alleged reference, applies to claims that recite method steps, and is required for establishing that the descriptive matter would inherently exist for every combination of a claim's limitation. *See In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326(CCPA 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.").

The Examiner correctly stated that Kolterman *et al.* (1996), which relates to normally thin type 1 diabetics, is silent about body weight. Although the Examiner appears to argue that it would have been inherent that any and every compound that delays gastric emptying will result in weight loss and thus be recognized as a treatment for obesity, there is no evidence to establish this and a retrospective view of alleged inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. *Smithkline Diagnostics v. Helena Laboratories Corp.*, 859 F.2d 878, 886-87, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988). It is well established that in deciding that a novel invention would have been obvious, there must be supporting teaching in the prior art. "That which may be inherent is not necessarily known. Obviousness cannot be

predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966).

There is, in any event, no suggestion or motivation in the prior art to combine these documents as combined by the Examiner, in order to obtain a method for the treatment of obesity, and the Examiner has not provided such a connection. *See In re Laskowski*, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398-99 (Fed. Cir. 1989); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). *See also Fromson v. Advance Offset Plate*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed. Cir. 1985) ("The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination.'"). Applicants respectfully request that the rejection of claims 1-6 as allegedly obvious within the meaning of 35 U.S.C. §103(a) over Kolterman *et al.* (1996) in view of Robert *et al.* be withdrawn.

The Fourth Rejection

Claims 1-6 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) or Kolterman *et al.* (PCT Publication No. WO95/07098) in view of Frishman *et al.* (Frishman, WH et al., Ed., In: *Cardiovascular Pharmacotherapeutics*, New York, Chapter 48, pp. 1093-1114 (February 1997)) or Weintraub *et al.* (*Nutrition Rev.*, 49:237-49 (1989)). In a telephonic interview dated October 30, 2002, the Examiner confirmed that the citation to "Weintraub *et al.* (*Nutrition Rev.*, 49:237-49 (1989))" was intended to be a citation to Bray (*Nutrition Rev.*, 49:33-45 (1991)). This rejection will be addressed accordingly, and is respectfully traversed.

The Examiner acknowledges that Kolterman *et al.* (1996) and Kolterman *et al.* ('098) are both "silent about the control of body weight" and the treatment of obesity.

The Examiner alleges, however, that Frishman *et al.* "taught amylin to have anorectic effect [*sic*]," and further asserts that Frishman *et al.* "taught the use of peripherally acting amylin as one of the innovative strategies to treat obesity," that "the administration of amylin both centrally and peripherally reduces food intake," and that amylin was "effective in reducing food intake in ob/ob and db/db mice." The Examiner also alleges that Weintraub *et al.* teaches the "slowing of gastric emptying by increasing gastric distension to inhibit food intake, as an approach for treating obesity." Based on these assertions, the Examiner concludes that one skilled in the art

> would have been motivated to produce the instant invention for the expected benefit of using Kolterman's (1996 and '098) method, not only to treat IDDM, but advantageously, for treating obesity as well, by making use of the anorectic and/or the anti-gastric emptying properties of Kolterman's (1996 and '098) pramlintide, since Frishman *et al.* expressly provides the motivation by teaching the use of peripherally acting amylin as one of the innovative strategies to treat obesity, or since Weintraub *et al.* expressly teach [sic] slowing of gastric emptying as an approach for treating obesity.

Applicants agree that the use of amylin is an "innovative" strategy to treat obesity. However, in all other respects, the rejection is respectfully traversed.

Applicants observe initially that the Examiner does not mention that Frishman *et al.* states that amylin "may be important in the insulin resistance found in obese patients" and that one patient with "an amylin-secreting pancreatic tumor was hypertensive, developed diabetes, and died of cerebral hemorrhage" (page 1107, col. 1). Frishman *et al.* concludes, furthermore, only that the potential role of amylin in weight reduction "awaits clinical investigation." Nevertheless, as noted above, the parent application to the instant case was filed on June 6, 1997. Applicants made their invention well prior to the February 1997 date indicated for Frishman *et al.* Although unnecessary, Applicants have filed a

Declaration under 37 C.F.R. § 1.131, which is deemed sufficient to remove this article as an alleged reference as well.

This leaves the Kolterman *et al.* (1996), Kolterman *et al.* ('098), and Bray (1991) documents cited by the Examiner. As noted above, and agreed by the Examiner, both Kolterman *et al.* (1996) and Kolterman *et al.* ('098) are silent about the control of body weight as well as treatment of obesity.

The Examiner asserts that the Kolterman *et al.* (1996) method induces "anorexia and delay in gastric emptying in human patients." As noted above, Kolterman *et al.* (1996) says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals. It states in a section entitled "Adverse Events" that the anorexia mentioned by the Examiner was a side effect that was not "considered serious." The paper concludes with no reference to weight or obesity, but with the statement that the observations from the study "will be extended in future studies to evaluate the extent to which amylin replacement can improve glucose control throughout the entire 24-h period." Thus Kolterman *et al.* (1996) does not contain a description of a "method of subcutaneous administration of pramlintide for treating obesity" as alleged by the Examiner. Furthermore, the Examiner has not provided any basis on which to believe that a non-serious side effect mentioned in a clinical study would or could form the basis of a determination by one skilled in the art at the time that it would constitute a method of treatment for a different indication.

Similarly, the Kolterman *et al.* '098 application does not contain a description of a "method of subcutaneous administration of pramlintide for treating obesity." It describes the results of a human clinical study in which pramlintide was administered to normally thin, insulin-using type 1 diabetics at a various doses over 14 days. The Examiner notes that the method resulted in a reduction in postprandial

glucose levels and delaying of gastric emptying. With regard to gastric emptying, however, the Kolterman et al. '098 application only describes the use of agents that delay gastric emptying, for example, as "diagnostic aids in gastro-intestinal radiologic examinations" (page 19) and for the "treatment of insulin-induced hypolyceamia" (page 19-20). The application also describes the use of amylins and amylin agonists for treatment of postprandial hyperglycemia (*i.e.*, high post-meal blood sugar; *e.g.*, page 21), for subjects undergoing a gastrointestinal diagnostic procedure (*e.g.*, page 23), and for treatment of subjects suffering from a gastrointestinal disorder (*e.g.*, page 23), post-prandial dumping syndrome (*e.g.*, page 23), or ingestion of a toxin (*e.g.*, page 24). The application does not mention the use of agents to delay gastric emptying in the treatment of obesity or for weight control.

Although the Examiner indicated that the citation to "Weintraub *et al.* (*Nutrition Rev.*, 49:237-49 (1989))" was intended to be a citation to Bray (*Nutrition Rev.*, 49:33-45 (1991)), Applicants note neither document supplies the missing link. Weintraub *et al.*, notes that there "is a great deal of controversy over the role of medications in the treatment of obesity," refers to the "negative views of anorexiant medications" and states that various "physicians, patients, and legislators see currently available anorexiant medications as harmful placebos" (page 237, first and second paragraphs; emphases added). In any event, the "anorexia" noted in Kolterman *et al.* was denominated as a side effect and not as a treatment.

Bray does not, as indicated by the Examiner, "expressly teach slowing of gastric emptying as an approach for treating obesity." Bray discusses the production of gastric distension as one of many approaches using, in particular, balloons. He states:

> Gastric and/or intestinal distension are important short-term signals to inhibit food intake. The intragastric balloon is one mechanism to produce chronic gastric

> distension. Current data do not support the effectiveness of gastric balloons as a treatment for obesity, probably because the stomach can stretch to maintain its relative capacity. A second approach is to slow gastric emptying. CCK has been proposed to work this way. Other drugs, such as aconitase, might also use this mechanism to produce satiety.

Bray concludes this discussion by stating that "[s]everal gastrointestinal peptides, including CCK, bombesin, and procolipase reduce feeding" and that "[o]ne approach to therapy would be to develop effective agonists for these peptide receptors." Bray notes in the following sentence, however, that "nutrients such as lactate, β-hydroxybutyrate and glucose" are "afferent signals to terminate eating" and appears to suggest, alternatively, the potential use of drugs that might prevent a drop in glucose that "precedes many spontaneous eating events in animals" or that "limit the early phase of insulin secretion" to treat obesity. Despite the fact that this catalog of alleged possibilities can hardly be said to suggest one over the other for purposes of evaluating obviousness – and the text cited by the Examiner certainly indicates no such preference – if CCK and it use to "slow gastric emptying" were a clear approach to the treatment of obesity, why are there no CCK agonists on the market today, eleven years after this publication? According to an update from Dr. Bray himself in a 2000 *Nature* review, "Peptide analogues of CCK have been developed, but none has reached the clinic, suggesting that they may have undesirable side effects" (emphasis added). Bray, G.A and Tartaglia, L.A., "Medicinal Strategies in the treatment of obesity," *Nature* 404:672-677 (2000).

Notwithstanding this failure, and setting aside for the moment the other articles referred to in the initial portion of this response relating to obesity, amylin and gastric emptying, which belie a conclusion of obviousness, Applicants note that there is no suggestion or motivation in the prior art to unite the above-noted documents as combined by the Examiner in order to obtain a method for the treatment of obesity, and the Examiner has not provided such a connection. *See In re Laskowski*, 871 F.2d 115, 117,

10 USPQ2d 1397, 1398-99 (Fed. Cir. 1989); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985). *See also Fromson v. Advance Offset Plate*, 755 F.2d 1549, 1556, 225 USPQ 26, 31 (Fed. Cir. 1985) ("The critical inquiry is whether 'there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination'."). This is particularly so in consideration of the fact that the anorexia relied on by the Examiner was viewed by Kolterman *et al.* as a side effect, and further in light the "negative views" of anorexic agents noted in Weintraub *et al.* and the failure of the CCK "gastric emptying" agonists briefly noted in Bray (1991).

It is well-settled that a selective combination of alleged prior art references must flow from a teaching contained in the cited documents. *Ashland Oil, Inc v. Delta Resins Refractories, Inc* ., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). As a result, "it is impermissible to use the claims as a frame and the [alleged] prior art references as a mosaic to piece together a facsimile of the claimed invention." *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051, 5 USPQ2d 1344 (Fed. Cir. 1998), *cert. denied*, 488 U.S. 825 (1988) (citing *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)). The Examiner's argument in support of the rejection essentially amounts to an impermissible hindsight argument, and the PTO has not met its burden of showing that the cited documents renders the claimed inventions obvious under the law.

There is no appreciation in any of the cited documents of the underlying basis of the invention, or recognition of the ability of amylins and amylin agonists to treat obesity. Nor does the unsupported statement of the Examiner that use of any agent that shows any anorectic or gastric-emptying action provide the missing link. Applicants note the absence of any supporting reference for this assertion.

The statement itself is very general, lacking any information regarding conditions of use or known limitations on such use, including any concomitant disadvantages. Moreover, there is no factual support for this overarching conclusion regarding anti-obesity pharmaceuticals. On the contrary, it is well understood that pharmaceutical products typically derive from extensive and costly research, and that such research precedes filing the patent application, which is then followed by years of costly development efforts before commercialization. Such is the case with the instant invention, which further belies a conclusion of obviousness at the time the invention was made. *See, e.g., In re Lunsford*, 148 USPQ 716, 720 (CCPA 1966) (Rich, J.) (nonobviousness supported by showing that the invention involved "the expenditure of vast amounts of research time and effort").

Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. §103(a) over Kolterman *et al.* (1996) or Kolterman *et al.* ('098) in view of Frishman *et al.* or Bray be reconsidered and withdrawn.

The Fifth Rejection

Claims 1-6 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kong *et al.* (Diabetologia, 40:82-88 (January 1997)) or MacDonald *et al.* (Diabetologia, 38(Supp. 1):A118 (1995)) in view of Robert *et al.* (PCT Publication No. WO91/16917), Jonderko *et al.* (Aliment. Pharmacol. Ther., 5:413-8 (1991)) and Frishman *et al.* (Frishman, WH et al., Ed., In: Cardiovascular Pharmacotherapeutics, New York, Chapter 48, pp. 1093-1114 (February 1997)) or Morley *et al.* (Pharmacol. Biochem. Behav., 44:577-80 (1993)). This rejection is respectfully traversed.

The Kong *et al.* document relates to clinical work of assignee Amylin Pharmaceuticals, Inc. As noted in the article, the next to last named author, Dr. Chris Moyses, was an Amylin Pharmaceuticals

employee. The Examiner asserts that Kong *et al.* teaches a method of infusion of an "effective amount" of pramlintide to human type 1 diabetic subjects and concludes that amylin or amylin agonist may be useful in improving glycaemic control by modifying gastric emptying.

The objective of Kong *et al.* was to "determine the effect of pramlintide on the rate of gastric emptying, superior mesenteric artery (SMA) blood flow, and 3-ortho-methylglucose (OMG) absorption in IDDM patients" (page 82). As with previous documents relied upon by the Examiner, the study related to normally thin type 1 diabetics and the Examiner acknowledges that Kong *et al.* says nothing about body weight, weight reduction, weight control, treatment of obesity, or the treatment of obese individuals. It also does not refer to the use of amylins or amylin agonists for controlling weight for cosmetic purposes, or controlling body weight to improve bodily appearance. The Examiner fails to note, however, that Kong *et al.* also states that the "extent of the delay of gastric emptying demonstrated in this trial probably represents an exaggerated pharmacological effect" and that further studies using doses "corresponding to a physiological amylin concentration are needed." Nevertheless, as noted above, the parent application to the instant case was filed on June 6, 1997, and Applicants made their invention well prior to the date indicated for Kong *et al.* Although unnecessary, Applicants have filed a Declaration under 37 C.F.R. § 1.131, which is deemed sufficient to remove this article as an alleged reference as well.

As noted above, and as agreed by the Examiner, MacDonald *et al.* also says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals, stating only that the infusion of pramlintide in this study "may be of value in regulating assimilation of ingested nutrients" in people with type 1 diabetes. The study was carried out, according to MacDonald *et al.*, to

assess whether delayed gastric emptying played a role in the ability of the amylin agonist pramlintide to reduce hyperglycemia. It was and is well known, as noted above, that IDDM (or type 1) patients are typically thin, not obese. Thus, there is no basis for the assertion that treatment of obesity is "inherent" in the MacDonald *et al.*, or that the method in MacDonald *et al.* "necessarily served as a method of treating obesity or inducing weight loss," as alleged by the Examiner in discussing this document.

None of Robert *et al.*, Jonderko *et al.* and Frishman *et al.* cannot save the rejection. As noted above, the Robert *et al.* patent application concerns the proposed use of Interleukin-1 to cure or prevent gastric ulcers and, allegedly, to prevent obesity by "retarding emptying of gastric contents [*sic*]" in order to reduce "a patient's desire for food" which is in turn may allegedly be "helpful in weight loss programs." Page 2, lines 22-26. It does not relate to amylin. The work allegedly undertaken and described in Robert *et al.* related primarily to gastroprotection and was based on rat studies in which Interleukin-1 was given to experimental rats who were killed shortly after administration, within one half hour to two hours, which is not sufficient time to evaluate weight change. Similarly, in the only experiment that allegedly related to gastric emptying, rats were killed 4 hours after Interleukin-1 administration, which is also an insufficient time to evaluate weight, treatment of "obesity," or alleged appetite reduction. Robert *et al.* unequivocally did not, as erroneously alleged by the Examiner at page 22 of the June 5, 2002 Office Action, "demonstrate[] that a gastric emptying-retarding compound also served as an anti-obesity agent by retaining food in the stromach of the treated individuals for prolonged periods of time, thus causing no desire to eat, thereby causing weight loss." In the Robert *et al.* "Example 2," which is a wholly prophetic example, the authors hypothesize only that Interleukin-1 "is presumed to act either by acting on appetite centers in the central nervous system, or by retarding the emptying of food from the stomach." Page 9, line 36 to page 10, line 2 (emphases added). Robert *et al.*

thus cannot be said to establish that "a gastric emptying-retarding compound also serves as an anti-obesity," as alleged by the Examiner, and its citation cannot complete the rejection of pending claims 1-6 and 11-15 under Section 103. *See also* Laviano, A. *et al.*, Peripherally Injected IL-1 Induces Anorexia and Increases Brain Tryptophan Concentrations," *Adv. Exp. Med. Biol.* 467:105-08 (1999), where the authors conclude at page 107 that, contrary to the assertions of the Examiner, "it is conceivable to reason that IL-1 may induce anorexia directly by acting on the serotonergic hypothalamic neurons, and indirectly by facilitating serotonergic activity, *i.e.*, enhancing brain [tryptophan] supply, the precursor of serotonin."

Similarly, as discussed above, Applicants note that Frishman *et al.* states that amylin "may be important in the insulin resistance found in obese patients" and that one patient with "an amylin-secreting pancreatic tumor was hypertensive, developed diabetes, and died of cerebral hemorrhage" (page 1107, col. 1), thus teaching away from the invention. Indeed, Frishman *et al.* concludes only that the potential role of amylin in weight reduction "awaits clinical investigation." Nevertheless, as noted above, the parent application to the instant case was filed on June 6, 1997, and, although believed to be unnecessary, Applicants have filed a Declaration under 37 C.F.R. § 1.131, which is deemed sufficient to remove this document as an alleged reference.

This leaves the Jonderko *et al.* and Morley *et al.* documents relied on by the Examiner. Jonderko *et al.* is alleged by the Examiner to "teach that gastric emptying rate [*sic*] influences the feeling of satiety" and that a "combination of an anorectic effect with the inhibition of gastric emptying can be considered a desirable feature of an anti-obesity agent." This document does not complete the rejection. Jonderko *et al.* reports on the effect of ephedrine, a stimulant that acts on the central nervous system.

Ephedrine is a sympathomimetic that acts directly and indirectly on the sympathetic nerves, with bronchodilating effects as the result of relaxation of bronchial smooth muscle through direct stimulation of ß adrenergic receptors. It is a nasal decongestant, and has been used therapeutically for nocturnal enuresis, diabetic neuropathic edema, dysmenorrhea, narcolepsy, and myasthenia gravis. Dollery C, editor. *Therapeutic drugs*. Churchill Livingstone Inc. New York: 1991; American Society of Health-System Pharmacists. American Hospital Formulary Service 95 Drug Information. ASHP. Bethesda, MD: 1995. Ephedrine is metabolized to norephedrine (phenylpropanolamine) which is responsible for the central nervous system stimulating effects of the drug. *Id.* Ephedrine in combination with caffeine was reportedly shown to promote thermogenesis, fat loss, and muscle gain in several trials. Astrup A, Toubro S. Thermogenic, metabolic, and cardiovascular responses to ephedrine and caffeine in man. *International Journal of Obesity and Related Metabolic Disorders* 1993; 17(suppl): S41-S43; Astrup A, Breum L. Pharmacological and clinical studies of ephedrine and other thermogenic agonists. *Obesity Research* 1995; 3(suppl4): 537S - 540S.

Although not discussed by the Examiner, it is understood that reports of adverse effects in adults of ephedrine and pseudoephedrine appeared in the medical literature in and outside of the United States prior to the publication of Jonderko *et al.* These effects included hypertension, hypotension, drug interactions, cardiovascular disturbances, and psychosis. Hirsch MS. Walter RM. Hasterlik RJ. Subarachnoid hemorrhage following ephedrine and MAO inhibitor. *JAMA* 1965. 194(11): 1259; Beary JF 3d. Pseudoephedrine producing postural hypotension in a pilot. *Aviation Space & Environmental Medicine* 1977; 48(4): 369; Roxanas MG. Spalding J. Ephedrine abuse psychosis. *Medical Journal of Australia* 1977; 2(19): 639-640; Dickerson J. Perrier D. Mayersohn M. Bressler R. Dose tolerance and pharmacokinetic studies of L (+) pseudoephedrine capsules in man. *European Journal of Clinical*

Pharmacology 1978; 14(4): 253-259; Rosen RA. Angina associated with pseudoephedrine. *Annals of Emergency Medicine* 1981; 10(4): 230-231; Mueller SM, Solow EB. Seizures associated with a new combination "pick-me-up" pill. *Annals of Neurology* 1982; 11(3):322.

The first report of fatal intracerebral hemorrhage due to ephedrine appeared in a case report in the *Annals of Neurology* in 1983 which described the case of a 20 year old male with intracerebral hemorrhage and vasculitis. Wooten MR, Khangure MS, Murphy MJ. Intracerebral hemorrhage and vasculitis related to ephedrine abuse. *Annals of Neurology* 1983; 13: 337-340. By 1985, another case report appeared of a non-fatal intracerebral hemorrhage following ingestion of a combination drug with ephedrine, phenylpropanolamine, and caffeine. Stoessl AJ, Young GB, Feasby TE. Intracerebral hemorrhage and angiographic beading following ingestion of catecholaminergics. *Stroke* 1985; 16(4):734-6. Between 1986 and 1993, several additional case reports appeared in the literature, including another case of ephedrine-induced cerebral hemorrhage in 1990 (Yin PA. Ephedrine-induced intracerebral hemorrhage and central nervous system vasculitis. *Stroke* 1990; 21(11): 1641), and three case reports of ephedrine consumption associated with stroke which appeared in the journal *Neurology* in 1993 (Bruno A, Nolte K, and Chapin J. Stroke associated with ephedrine use. *Neurology* 1993; 43:1313-1316).

As the number of adverse events relating to ephedrine continued to escalate, some states began to enact regulatory controls, with Ohio banning the sale of all ephedrine-containing products in 1994. Lambert B. Nassau enacts weakened ban on herbal stimulant. *New York Times*. Tuesday May 14 1996. Section B, Page 1. By July 1995, fourteen states had placed some control or restriction on ephedrine, including some that banned over-the-counter sales. *Federal Register* July 27 1995. Volume 60, Number

144. Page 38643-38647. In October 1995, the FDA Food Advisory Committee released a statement reporting more than 330 adverse effects and 12 deaths due to ephedrine. Associated Press. FDA debates safety of diet Supplements. *The New York Times* October 13 1995. Section A, Page 30.

As the Examiner may be aware, ephedrine is found in various products that the FDA believes that it may be related to more than 50 deaths. Most of the serious injuries involve high blood pressure that can cause bleeding in the brain, a stroke or a heart attack. As of March 1997, ephedrine products were banned or restricted in at least 20 states. This is hardly a basis on which to claim that it would have been obvious to use, for the treatment of obesity, an unrelated compound being investigated for the treatment of diabetes that has effects on gastric emptying. Indeed, contrary to the concept of gastric emptying as mechanism for ephedrine, Jonderko *et al.* expressly states that "an influence of ephedrine on structures regulating food intake within the central nervous system cannot be excluded" (page 416-417). Jonderko *et al.* conclude in their 1991 article only that ephedrine – the same compound known to cause death and other serious injuries – may be "an interesting candidate for trials of pharmacological support of a 'classical' weight-reducing treatment involving restriction of energy intake" (page 417).

Neither can Morley *et al.* save the rejection. The Examiner claims that Morley *et al.* "showed that amylin is a peripheral anorectic peptide" and "that administration to a mammal decreased or suppressed food intake." Morley *et al.* note, however, that they failed to see food intake suppression in various groups of experimental animals (page 579). They conclude, furthermore, that their rat data does not support a role of amylin in the development of anorexia seen in older animals as there was no marked change in the dose-response (page 579). The Morley *et al.* article also notes that amylin "has been postulated to play a role in the pathogenesis of Type II diabetes mellitus" (page 577), and it is

silent as to the use of amylin for weight reduction, weight control, treatment of obesity, or treatment of obese individuals.

The Examiner nevertheless asserts, using a combination of these six documents – the first and second relating to clinical study of pramlintide in type 1 diabetics (Kong *et al.* and MacDonald *et al.*), the third relating to the IL-1 cytokine (Robert *et al.*), the fourth relating to ephedrine, a drug whose mechanism of action was unknown and that has been withdrawn from the market because it kills people (Jonderko *et al.*), the fifth reviewing past, present and possible future treatments for obesity (Frishman *et al.*), and the sixth alleging amylin to be a short term "peripheral anorectic agent" in certain animals but providing no evidence or suggestion of weight loss (and two of which (Kong *et al.* and Frishman *et al.*) are not references at all – that one "skilled in the art" would have been motivated to produce the claimed inventions by using Kong *et al.*'s or MacDonald *et al.*'s method as allegedly taught by Jonderko *et al.*

The Examiner's attempts to establish obviousness are based not only on an improper standard (one "skilled in the art") but on multiple unrelated references, as well as on presuppositions that the person of ordinary skill would necessarily pick and choose among the multitude of disclosures to combine them.[16] This is insufficient to meet the PTO's burden of proof. In *Polaroid Corp. v. Eastman Kodak Co.*, 789 F.2d 1556, 1571, 229 USPQ 561 (Fed. Cir.), *cert. denied*, 479 U.S. 850 (1986), the court held:

[16] "The question in a §103 case is what the references would collectively suggest to one of ordinary skill in the art. *E.g.*, *In re Ehrreich and Avery*, 200 USPQ 504 (CCPA 1979); *In re Simon*, 461 F.2d 1387, 174 USPQ 114 (CCPA 1972). "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *See, e.g.*, W.*L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 313 (Fed. Cir. 1983)." *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (emphasis added). In a section 103 analysis, the evidence must be viewed from the position of a person of ordinary skill, not from the position of an expert. *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050, 5 USPQ2d 1434, 1438 (Fed. Cir. 1998), *cert. denied*, 488 U.S. 825 (1988).

> Thus Kodak would have us pick and choose individual elements from three prior art patents and thereby re-create the invention.... Kodak does not tell us, however, what there is in the three prior patents that would have suggested such picking and choosing at the time the invention was made.

Referring to the discussion in the introductory portions of this Response, Applicants note that for purposes of §103, a "person of ordinary skill in the art is presumed to be one who thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate." *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 455, 227 USPQ 293 (Fed. Cir. 1985). Another major deficiency of the Examiner's rejection is that it necessarily relies on Applicants' own work as a road map to construe and combine the alleged prior art in a way which would allegedly lead to obviousness.

Under §103, the invention must be shown to have been obvious by the suggestions of the alleged prior art itself, and without resort to the road map approach of utilizing the application before the PTO. The Federal Circuit stated, "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. ... One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to depreciate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596 (Fed. Cir. 1988) (quoting *W.L. Gore Associates Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 [220 USPQ 303 (Fed. Cir. 1983)). *Accord Grain Processing Corp. v. American Maize Prod. Co.*, 840 F.2d 902, 907, 5 USPQ2d 1788 (Fed. Cir. 1988) ("Care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit"); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1574-75, 1 USPQ2d 1593 (Fed. Cir.), *cert. denied*, 481 U.S.

1052 (1987); *Orthopedic Equipment Co. v. United States*, 702 F.2d 1005, 1012, 217 USPQ 193 (Fed. Cir. 1983).

In determining the scope and content of the prior art, and determining whether the prior art suggested the claimed invention, the alleged references "must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention." *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1481, 1 USPQ2d 1241 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909 (1987); *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1568, 1 USPQ2d 1593 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987) (an alleged prior art reference "must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the invention"). The teachings of the documents are to be applied in the context of their significance to a technician at the time – a technician without knowledge of the solution. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143, 227 USPQ 543 (Fed. Cir. 1985). In this case, for reasons noted above and throughout this Response, Applicants submit that the documents argued by the Examiner are not only unrelated and not discussed within the context of the art as a whole, but are also in many ways antithetical in concept to the claimed invention and to each other, and, thus, cannot form a basis for determining the claims obvious within the meaning of the law.

Applicants respectfully request that the rejection of claims 1-3 under 35 U.S.C. §103(a) over Kong *et al.* or MacDonald *et al.* in view of Robert *et al.*, Jonderko *et al.* and Frishman *et al.* or Morley *et al.* be reconsidered and withdrawn.

The Sixth Rejection

Claims 1-6 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kolterman *et al.* (PCT Publication No. WO95/07098) or Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) in view of Morley *et al.* (Pharmacol. Biochem. Behav., 44:577-80 (1993)) and Jonderko *et al.* (Aliment. Pharmacol. Ther., 5:413-8 (1991)). This rejection is respectfully traversed.

Each of these documents has been discussed above. The Examiner acknowledges that Kolterman *et al.* (1996) and Kolterman *et al.* ('098) are both "silent about the control of body weight" and the treatment of obesity. Indeed, as noted above, Kolterman *et al.* (1996) says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals, stating only in a section entitled "Adverse Events" that the anorexia mentioned by the Examiner was a side effect that was not "considered serious." The paper concludes with no reference to weight or obesity, but with the statement that the observations from the study "will be extended in future studies to evaluate the extent to which amylin replacement can improve glucose control throughout the entire 24-h period." Thus, Kolterman *et al.* (1996) does not contain an "implicit" description of a "method of treating obesity" as alleged by the Examiner. Furthermore, the Examiner has not provided any basis on which to believe that a non-serious side effect mentioned in a clinical study would or could form the basis of a determination by one skilled in the art at the time that it would constitute a method of treatment for a different indication.

Similarly, the Kolterman *et al.* '098 application does not contain a description of a "method of treating obesity." It describes the results of a human clinical study in which pramlintide was administered to insulin-using type 1 diabetics at a various doses over 14 days. The Examiner notes that the method results in a reduction in postprandial glucose levels and delaying of gastric emptying. As

noted above, however, the Kolterman et al. '098 application does not mention the use of agents to delay gastric emptying in the treatment of obesity or for weight control. It describes the use of agents that delay gastric emptying, for example, as "diagnostic aids in gastro-intestinal radiologic examinations" (page 19) and for the "treatment of insulin-induced hypolyceamia" (page 19-20), and the use of amylins and amylin agonists for treatment of postprandial hyperglycemia (*i.e.*, high post-meal blood sugar; *e.g.*, page 21), for subjects undergoing a gastrointestinal diagnostic procedure (*e.g.*, page 23), and for treatment of subjects suffering from a gastrointestinal disorder (*e.g.*, page 23), post-prandial dumping syndrome (*e.g.*, page 23), or ingestion of a toxin (*e.g.*, page 24).

The Examiner repeats the assertion that Morley *et al.* "showed that amylin is a peripheral anorectic peptide" and "that administration to a mammal decreased or suppressed food intake." As indicated above, the Morley *et al.* article notes, however, that the effect was only short term and that they failed to see food intake suppression in various groups of experimental animals (page 579). Morley *et al.* concludes, furthermore, that the data did not support a role of amylin in the development of anorexia seen in older animals as there was no marked change in the dose-response (page 579). The Morley *et al.* article also notes that amylin "has been postulated to play a role in the pathogenesis of Type II diabetes mellitus" (page 577), and it is silent as to the use of amylin for weight reduction, weight control, treatment of obesity, or treatment of obese individuals.

Jonderko *et al.* (1989) has nothing to do with amylin, but is alleged by the Examiner to teach "that anorectic agents that delay GE or gastric emptying might contribute to progress in the treatment of obesity." As noted above, Jonderko *et al.* reports on the effect of ephedrine, a stimulant acting on the central nervous system that has been shown to cause hypertension, hypotension, drug interactions,

cardiovascular disturbances (including vasculitis and intracerebral hemorrhage), psychosis, and death, and has reportedly been banned in or restricted in at least 20 states. This is hardly a basis on which to claim that it would have been obvious to use amylin and amylin agonists for treating obesity. Indeed, Jonderko *et al.* expressly state that "an influence of ephedrine on structures regulating food intake within the central nervous system cannot be excluded" (page 416-417). Jonderko *et al.* conclude in their 1991 article that ephedrine – a same compound now known to cause death and other serious injuries – may be "an interesting candidate" for clinical trials (page 417).

For reasons noted above, Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. §103(a) over Kolterman *et al.* (PCT Publication No. WO95/07098) or Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) in view of Morley *et al.* (Pharmacol. Biochem. Behav., 44:577-80 (1993)) and *Jonderko et al.* (Aliment. Pharmacol. Ther., 5:413-8 (1991)) be reconsidered and withdrawn.

The Seventh Rejection

Claims 1-6 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kolterman *et al.* (PCT Publication No. WO95/07098) or Kolterman *et al.* (Diabetologia, 39:492-9 (1996)) in view of Frishman *et al.* (Frishman, WH et al., Ed., In: Cardiovascular Pharmacotherapeutics, New York, Chapter 48, pp. 1093-1114 (February 1997)) and Jonderko *et al.* (Israel J. Med. Sci., 25:20-24 (1989)) or Guthrie *et al.* (U.S. Patent No. 4,443,619). This rejection is respectfully traversed.

Each of the Kolterman *et al.* ('098), Kolterman *et al.* (1996), Frishman *et al.* and Guthrie *et al.* documents has been discussed above.

The Examiner has acknowledged that Kolterman *et al.* (1996) and Kolterman *et al.* ('098) are both "silent about the control of body weight" and the treatment of obesity. Kolterman *et al.* (1996) says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals. It states only in a section entitled "Adverse Events" that the anorexia mentioned by the Examiner was a side effect that was not "considered serious." The paper concludes with no reference to weight or obesity, but states that the observations from the study "will be extended in future studies to evaluate the extent to which amylin replacement can improve glucose control throughout the entire 24-h period." Thus, Kolterman *et al.* (1996) does not contain an "implicit" description of a "method of treating obesity" as alleged by the Examiner. Furthermore, the Examiner has not provided any basis on which to believe that a non-serious side effect mentioned in a clinical study would or could form the basis of a determination by one skilled in the art at the time that it would constitute a method of treatment for a different indication.

Similarly, the Kolterman *et al.* '098 application does not contain a description of a "method of treating obesity." The Examiner notes that the method results in a reduction in postprandial glucose levels and delaying of gastric emptying. With regard to gastric emptying, however, the Kolterman et al. '098 application describes the use of agents that delay gastric emptying, for example, as "diagnostic aids in gastro-intestinal radiologic examinations" (page 19) and for the "treatment of insulin-induced hypolyceamia" (page 19-20). The application also describes the use of amylins and amylin agonists for treatment of postprandial hyperglycemia (*i.e.*, high post-meal blood sugar; *e.g.*, page 21), for subjects undergoing a gastrointestinal diagnostic procedure (*e.g.*, page 23), and for treatment of subjects suffering from a gastrointestinal disorder (*e.g.*, page 23), post-prandial dumping syndrome (*e.g.*, page

23), or ingestion of a toxin (*e.g.*, page 24). The application does not mention the use of agents to delay gastric emptying in the treatment of obesity or for weight control.

The Examiner alleges that Guthrie *et al.* teaches or suggests "that anorectic or appetite-suppressing agents that delay gastric emptying" are useful in the treatment of obesity. Guthrie *et al.* was published prior to the discovery of both amylin and pramlintide. Additionally, although not necessary to establish that the rejection is properly withdrawn, Applicants note the patent shows that certain rats given the claimed compounds gained weight or did not reduce their food consumption. *See, e.g.*, "Example 6 [*sic*, 16]" of the Guthrie *et al.* patent showing that rats given a chlorocitric acid of the invention gained weight. Still other results indicate that the food intake of rats in certain experiments were also no different from control. This document does not establish that any and all compounds having any gastric emptying activity are necessarily useful for treating obesity, let alone one that is being evaluated for use in the treatment of diabetes and was reported to cause a non-serious, anorexic side effect in some patients.

As noted above, Frishman *et al.* states that amylin "may be important in the insulin resistance found in obese patients" and that one patient with "an amylin-secreting pancreatic tumor was hypertensive, developed diabetes, and died of cerebral hemorrhage" (page 1107, col. 1), and thus may be viewed as teaching away from the invention. Indeed, Frishman *et al.* concludes only that the potential role of amylin in weight reduction "awaits clinical investigation." Nevertheless, as noted above, the grandparent application to the instant case was filed on June 6, 1997. Applicants made their invention well prior to the February 1997 date indicated for Frishman *et al.* Although unnecessary, Applicants

have filed a Declaration under 37 C.F.R. § 1.131 that is believed suffient to remove this document as an alleged reference.

This leaves the Jonderko *et al.* (1989) document. This citation is of even less relevance than Jonderko (1991). Jonderko *et al.* (1989) has nothing to do with amylin and does not describe weight loss with the subject compound, "mazindol." Mazindol is a sympathomimetic amine similar to an amphetamine that stimulates the central nervous system, thus increasing the heart rate and blood pressure and decreasing appetite.

In the introduction to Jonderko *et al.* (1989), the authors compare mazindol favorably to fenfluramine, which is referred to as "a centrally acting anorectic" that "delays [gastric emptying] in some animals" (page 20, col. 2). In September 1997, several months after Applicants' application for patent was filed, acting on evidence about significant side-effects associated with fenfluramine (as well as dexfenfluramine), the Food and Drug Administration requested that manufacturers withdraw both treatments for obesity from the market. The action was based on findings from doctors who evaluated patients taking these two drugs with echocardiograms and showed that approximately 30 percent of patients who were evaluated had abnormal echocardiograms, even though they had no symptoms. September 15, 1997 Food And Drug Administration Press Release (P97-32). At the time of the withdrawal of the drugs, the FDA urged the public to stop taking the drug and recommended that anyone exposed to the drug consult a physician about possible damage to their heart.

Although not mentioned by the PTO, Jonderko *et al.* (1989) observed that statistically significant differences in gastric emptying "were not observed until 80 min. from the start of GE examination" (page 22, col. 2). Additionally, contrary to the conclusion of the Examiner that Jonderko *et al.* (1989)

teaches that "anorectic agents that delay gastric emptying" are suggested "for the treatment of obesity," the authors state only that, "Since gastric distension modulates satiety, a linkage between the inhibitory influence on [gastric emptying] of a drug and its anorectic effect could be hypothesized" (page 23, col. 1). The authors conclude, furthermore, that their study "does not answer the question whether the delay of [gastric emptying] that occurred after administration of a single mazindol dose would be removed by tachyphylaxis" (page 23, col. 1). As the Examiner is likely to be aware, tachyphylaxis may be defined as a rapidly decreasing response to a drug following administration of the initial doses.

Indeed, the WHO Pharmaceuticals Newsletter (Nos. 5&6, May & June 1997), published at about the time Applicants' application for patent was filed, contains a report on regulatory actions regarding restrictions on the use of anorectic agents. It was reported that the European Committee on Proprietary Medicinal Products reviewed the overall risk-benefit of anorectic agents in the treatment of obesity, and in particular the risk of the occurrence of primary pulmonary hypertension. Two categories of anorectic agent were assessed, including "amphetamine-like" compounds such as mazindol, among others. The Committee concluded that studies confirm the risk of the occurrence of primary pulmonary hypertension, but determined that the risk-benefit balance was favorable provided that certain restrictions were met, including (1) restriction of use as adjunctive therapy to dietary measures in patients with major obesities with a body mass index of 30 kg/m2 or higher; (2) restriction to a duration of treatment from 4 to 6 weeks with a maximum duration of 3 months because of the increased risk of primary pulmonary hypertension; and (3) the provision of clear information on the potentially fatal risk of primary pulmonary hypertension related to the intake of anorectic agents is made available both to the physician and the patient. Communication from the EMEA dated 4 November 1996, enclosing the Committee for Proprietary Medicinal Products Assessment Report for Anorectic Agents, London, 18

July 1996. *See also* Pharmaceuticals Newsletter No. 8, August 1995, No. 10, October 1996 and Nos. 3&4, March & April 1997.

There is no known connection between the claimed invention and mazindol and potentially fatal compounds such as fenfluramine. And there is no basis for concluding that any and every compound that has an action on gastric emptying is necessarily a treatment for obesity. The Federal Circuit has made it clear that each invention must be judged on its merits and that it is impermissible to conclude, as the Examiner has here, that all patents for all future inventions are foreclosed simply because there are one or more published articles regarding the overall subject, in this case alleged possible treatments for obesity that may have some activity on gastric emptying. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc* ., 802 F.2d 1367, 1379, 231 USPQ 81, 90-91 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987) ("The district court's finding that Kohler and Milstein developed a method for producing monoclonal antibodies *in vitro* is correct, but that finding proves no more; although it made possible all later work in that it paved the way for a supply of monoclonal antibodies, it indisputably does not suggest using monoclonal antibodies in a sandwich assay in accordance with the invention claimed in the '110 patent.").

As the Examiner is also aware, and as noted above, there is no basis for reaching a conclusion of obviousness within the meaning of 35 USC §103 on the basis that it would have been "obvious to try" the use of amylin agonists for treatment of obesity based on reported activity regarding gastric emptying. While the cited documents do not establish even that it would have been obvious to try amylin agonists for the treatment of obesity, the Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 USC §103. *See In re Dow Chemical Co.*, 837 F.2d, 469, 473, 5

USPQ2d 1529, 1532 (Fed. Cir. 1985) ("The PTO presents, in essence, an 'obvious to experiment' standard for obviousness. However, selective hindsight is no more applicable to the design of experiments than it is to the combination of prior art teachings. There must be a reason or suggestion in the art for selecting the procedure used, other than the knowledge learned from the applicant's disclosure."); *In re Tomlinson*, 363 F.2d 928, 931, 150 USPQ 623, 626 (CCPA 1966) ("The examiner, . . . [said] 'it would be obvious for a skilled chemist to try . . . citing *In re Moreton* . . . for the proposition that obviousness does not require absolute predictability. Our reply to this view is simply that it begs the question, which is obviousness under section 103 of compositions and methods, not of the direction to be taken in making efforts or attempts. Slight reflection suggests, we think, that there is usually an element of 'obviousness to try' in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research'.").

Applicants also reiterate that the Rink *et al.* '590 anorexia patent (U.S. Pat. No. 5,656,590 issued August 12, 1997 for "Treatment of anorexia and related states"), under "Description of Preferred Embodiments," teaches away from Applicants' invention by reporting that treatment with amylin likely has no useful effect on the weight of an animal:

> [A]pplicant believes that the appetite suppressant effects of amylin is seen only at very high doses and may be short lived. Indeed, applicant has discovered that in toxicological studies with amylin in both rats and dogs, where two weeks of amylin administration were used, there was no reduction in food intake or weight in the animal [emphasis added].

The Rink '590 patent describes and claims methods for the treatment of patients suffering from anorexia or a similar condition by administering an amylin or an amylin analogue in order to increase, not lose, weight.

Applicants respectfully request that the rejection of claims 1-6 under 35 U.S.C. §103(a) over Kolterman *et al.* ('098) or Kolterman *et al.* (1996) in view of Frishman *et al.* and Jonderko *et al.* (1989) or Guthrie *et al.* (U.S. Patent No. 4,443,619), be reconsidered and withdrawn.

The 35 U.S.C. §112, First Paragraph, Rejection

Claims 1-6 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the term "anti-obesity agent" in amended claim 1 lacks "descriptive support in the instant specification," and concludes that it is "new matter" (citing *In re Rasmussen*, 650 F.2d 1212 (CCPA 1981)).

The *American Heritage® Dictionary of the English Language* defines the prefix "anti-" to mean "opposing" or "counteracting." The present application states that the invention is directed to "novel methods for treating or preventing obesity" and describes methods to decrease body weight. The methods involve administration of an amylin or an amylin agonist, and the application at page 13 goes on to state that "treating or preventing" obesity includes "combating" or "eliminating" the disease. It can hardly be argued that combating or eliminating obesity are not actions that oppose or counteract obesity. It is thus equally plain that the amylins and amylin agonists administered in the described and claimed methods for treatment of obesity that decrease weight may thus be referred to as "anti-obesity agents." The Abstract expressly refers to a therapeutically effective amount of an amylin or an amylin agonist" of the invention as an "obesity relief agent."

There can be no doubt that the "disclosure of the application relied upon reasonably conveys to the artisan that the inventor had possession" of an "anti-obesity agent." *See, e.g., Wang Labs., Inc. v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1766, 1774 (Fed. Cir. 1993) (recitation of "support means for supporting the memory module at an angle with respect to the printed circuit motherboard" adequately supported by the original application); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) (summary judgment of invalidity for alleged failure to comply with written description requirement reversed); *In re Rasmussen*, 650 F.2d 1212, 1215, 211 USPQ 323, 327 (CCPA 1981) (phrase "adheringly applying" adequately supported by specification, and 112 rejection reversed).

The presently claimed invention satisfies 35 U.S.C. §112, first paragraph, and reconsideration and withdrawal of this rejection is respectfully requested.

The 35 U.S.C. §112, Second Paragraph, Rejection

Claims 1-6 stand rejected under 35 U.S.C. §112, second paragraph. The Examiner alleges that the word "effective" in the phrase "effective amount" – a phrase used in the claims of more than 26,000 patents issued by the PTO since 1996 alone – "renders the claim indefinite."

Applicant respectfully submits that under the law of indefiniteness, the Examiner's rejection is appropriate. Determining whether a claim is indefinite requires an analysis of "whether one skilled in the art would understand the bounds of the claim when read in light of the specification. . . . If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, [section] 112 demands no more." *Miles Lab., Inc. v. Shandon Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), *cert. denied*, 114 S. Ct. 943 (1994); *see also Hybritech Inc. v.*

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94-95 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). So it is with the instant case.

Given the teachings of the specification, one of ordinary skill in the art can readily understand the metes and bounds of the claimed invention. The claim reference to an "effective amount" is plainly a reference to an amount effective to treat or prevent obesity, as set forth in the claim. There is no other amount foreseen by the claims and the meaning is clear. As stated in *In re Borkowski*, 442 F.2d 904, 909, 164 USPQ 642, 645-46 (CCPA 1970) (footnotes omitted, emphasis in original):

> The first sentence of the second paragraph of §112 is essentially a requirement for precision and definiteness of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends the claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

The U.S. Court of Appeals for the Federal Circuit recently reiterated its standard for assessing whether a patent claim is sufficiently definite to satisfy 35 U.S.C. §112, second paragraph, in *Exxon Research and Engineering Co. v. U.S.*, 60 USPQ2d 1272 (September 19, 2001). Therein, citing *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875, 27 USPQ2d 1123, 1126 (Fed. Cir. 1993), the Court stated: "If one skilled in the art would understand the bounds of the claim when read in light of the specification, then the claim satisfies section 112 paragraph 2."

Indeed, the Federal Circuit has specifically recognized the appropriateness of claims containing the phrase "effective amount," *see, e.g., Eli Lilly and Co. v. Barr Laboratories Inc.*, 58 USPQ2d 1869 (Fed. Cir. 2001), as did its predecessor court, the CCPA. *See, e.g., In re Watson*, 186 USPQ 11, 20 (CCPA 1975) (on consideration of rejection based on alleged indefiniteness of "effective amount" as used in the phrase "an effective amount of a germicide suitable for use in oral hygiene," the Court

reversed, holding that the "very term 'germicide,' used in this claim, indicates that germicidal action is the effect sought to be produced," and those "skilled in the art will be able to determine from the disclosure, including the examples, what an effective amount of germicide is").

The PTO has argued but provided no evidence that one "skilled in the art" would not understand the term "effective" as used in the instant application. *See Rhone-Poulenc Agrochimie S.A. v. Biagro Western Sales Inc.*, 35 USPQ2d 1203, (E.D. Cal. 1994) (discarding unsupported argument that patent failed to comply with the "full, clear, concise, and exact terms" requirement of 35 U.S.C. Section 112 in use of the phrase "fungicidally effective"). *See also Ex parte Skuballa*, 12 USPQ2d 1570, 1571 (BdPatApp&Int 1989) (Examiner's rejection of application claim for pharmaceutical composition containing prostacyclin derivatives, and method claims for administering such compositions to patient, on ground that claims are indefinite for failing to state function to be achieved by "effective amount" of active ingredient present, is reversed, since method claims set forth functions to be achieved by administration of claimed compounds, and since composition claim is definite when read in light of specification).

The presently claimed invention satisfies 35 U.S.C. §112, second paragraph, and reconsideration and withdrawal of this rejection is respectfully requested.

The Double Patenting Rejections

The First Rejection

While acknowledging that Applicants requested the rejection be held in abeyance until official notification of allowance, the Examiner maintained a rejection of claims 1-6 under the judicially created doctrine of obviousness type double patenting over claims 1-15 of co-pending U.S. Application Serial

Number 09/445,517. The Manual of Patent Examining Procedure §804.02, citing Quad Environmental Technologies Corp. v. Union Sanitary District, F.2d 870, 20 USPQ2d 1392 (Fed. Cir. 1991), states that the "filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection." Given that fact, and the fact that the term of any patent issuing from the subject application and that of U.S. Application Serial No. 09/445,517 would be the same, a terminal disclaimer will be filed upon withdrawal of all other outstanding rejections and objections in the present matter.

The Second Rejection

Claims 1-6 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-25 of Kolterman *et al.* (U.S. Patent No. 6,114,304) in view of Weintraub *et al.* (Nutrition Rev., 49:237-49 (1989)) and Robert *et al.* (PCT Publication No. WO91/16917).

A rejection for obviousness-type double patenting can only be sustained where claims are directed merely to an obvious variation of an invention disclosed and claimed in an earlier patent by the same inventor. *See General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1278, 23 USPQ2d 1839, 1843 (Fed. Cir. 1992); *In re Vogel*, 422 F.2d 438, 442, 164 USPQ 619, 622 (CCPA 1970). Generally, a "one-way" test has been applied to determine obviousness-type double patenting. Under that test, the examiner asks whether the application claims are obvious over the patent claims. *In re Berg*, 46 USPQ2d 1226, 1229 (Fed. Cir. 1998).

Obviousness-type double patenting entails a two-step analysis. First, as a matter of law, the claim of the earlier patent and the claim in the later application are construed, and the later claim is overlaid on the earlier claim to determine whether the later claim encompasses subject matter previously

claimed. *See Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326, 52 USPQ2d 1590, 1593 (Fed. Cir. 1999) (stating that "analysis of the claims is the first step" in an obviousness-type double patenting inquiry); *General Foods Corp. v. Studiengesellschaft Kohle*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1844 (Fed. Cir. 1992). Second, it must be determined whether the differences in subject matter between the two claims is such that the claims are patentably distinct. *See Georgia-Pacific*, 195 F.3d at 1327, 52 USPQ2d at 1595 (proceeding to determine whether differences between the two claims are patentably distinct after construing the claims); *General Foods*, 972 F.2d at 1279, 23 USPQ2d at 1844 (explaining that the terms "patentably distinguishable," "patentable distinctions," and obvious variations are equivalent for analytical purposes).

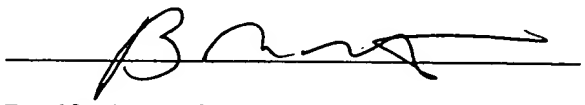
Here, however, the later claims of the instant application do not encompass subject matter previously claimed because the Kolterman *et al.* '304 patent, entitled "Methods for regulating gastrointestinal motility," is not directed to treatment of obesity. The '304 patent, says nothing about body weight, weight reduction, weight control, treatment of obesity, or treatment of obese individuals, other than to note that post-food amylin levels in "obese, insulin-resistant individuals" can be increased, thus teaching away from the administration of an amylin or an amylin agonist to treat obesity. Accordingly, while the focus of double patenting rejections is the claims of the application and patent and, in setting forth this rejection, the PTO has not addressed the claims of the cited documents, nor the relationship of the pending claims to those claims, Applicants note the lack of relationship between the claims. Various documents cited by the PTO relating to pramlintide and gastric emptying have been addressed above, as have Weintraub *et al.* and Robert *et al.*, in discussing the nonobviousness of the claimed invention. In view of the foregoing, and Applicants' previous remarks, withdrawal of this rejection for alleged obviousness-type double patenting is respectfully requested.

CONCLUSION

In conclusion, Applicants respectfully submit that all pending claims are in condition for allowance. The Examiner is invited to contact Applicants' undersigned Representative if it is believed that prosecution may be furthered thereby.

Respectfully Submitted,

Date: December 2, 2002



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MARKED UP COPY OF REWORD PARAGRAPHS OF THE SPECIFICATION

Please reword the paragraph bridging pages 19-20 of the originally filed application as follows:

--The receptor binding assay, a competition assay which measures the ability of compounds to bind specifically to membrane-bound amylin receptors, is described in United States Patent No. 5,264,372, issued November 23, 1993, the disclosure of which is incorporated herein by reference. The receptor binding assay is also described in Example 2 below. A preferred source of the membrane preparations used in the assay is the basal forebrain which comprises membranes from the nucleus accumbens and surrounding regions. Compounds being assayed compete for binding to these receptor preparations with ^{125}I Bolton Hunter rat amylin. Competition curves, wherein the amount bound (B) is plotted as a function of the log of the concentration of ligand are analyzed by the computer, using analyses by nonlinear regression to a 4-parameter logistic equation ([Inplot] INPLOT program; [GraphPAD] GRAPHPAD Software, San Diego, California) or the ALLFIT program of DeLean et al. (ALLFIT, Version 2.7 (NIH, Bethesda, MD 20892)). Munson and Rodbard, Anal. Biochem. 107:220-239 (1980).--

Please reword the paragraph bridging pages 23-24 of the originally filed application as follows:

--Peptides may be purified by RP-HPLC (preparative and analytical) using a Waters [Delta Prep] DELTA PREP 3000 system. A C4, C8 or C18 preparative column (10 μ, 2.2 X 25 cm; Vydac, Hesperia, CA) may be used to isolate peptides, and purity may be determined using a C4, C8 or C18 analytical column (5 μ, 0.46 X 25 cm; Vydac). Solvents (A=0.1% TFA/water and B=0.1% TFA/CH_3CN) may be delivered to the analytical column at a flowrate of 1.0 ml/min and to the preparative column at 15 ml/min. Amino acid analyses may be performed on the Waters [Pico Tag] PICO TAG system and processed using the [Maxima] MAXIMA program. Peptides may be hydrolyzed by vapor-phase acid hydrolysis (115°C, 20-24 h). Hydrolysates may be derivatized and analyzed by standard methods (Cohen, et al., The Pico Tag Method: A Manual of Advanced Techniques for Amino Acid Analysis, pp. 11-52, Millipore Corporation, Milford, MA (1989)). Fast atom bombardment analysis may be carried out by M-Scan, Incorporated (West Chester, PA). Mass calibration may be performed using cesium iodide or cesium iodide/glycerol. Plasma desorption ionization analysis using time of flight detection may be carried out on an Applied Biosystems [Bio-Ion] BIO-ION 20 mass spectrometer.--

Please reword the second paragraph on page 27 of the originally filed application as follows:

--If desired, solutions of the above compositions may be thickened with a thickening agent such as methyl cellulose. They may be prepared in emulsified form, either water in oil or oil in water. Any of a wide variety of pharmaceutically acceptable emulsifying agents may be employed including, for example, acacia powder, a non-ionic surfactant (such as a [Tween] TWEEN), or an ionic surfactant (such as alkali polyether alcohol sulfates or sulfonates, e.g., a [Triton] TRITON).--

Please reword the first full paragraph on page 34 of the originally filed application as follows:

--To measure ^{125}I-amylin binding, membranes from 4 mg original wet weight of tissue were incubated with ^{125}I-amylin at 12-16 pM in 20 mM HEPES buffer containing 0.5 mg/ml bacitracin, 0.5 mg/ml bovine serum albumin, and 0.2 mM PMSF. Solutions were incubated for 60 minutes at 23°C. Incubations were terminated by filtration through GF/B glass fiber filters (Whatman Inc., Clifton, NJ) which had been presoaked for 4 hours in 0.3% [poylethyleneimine] polyethyleneimine in order to reduce nonspecific binding of radiolabeled peptides. Filters were washed immediately before filtration with 5 ml cold PBS, and immediately after filtration with 15 ml cold PBS. Filters were removed and radioactivity assessed in a gamma-counter at a counting efficiency of 77%. Competition curves were generated by measuring binding in the presence of 10^{-12} to 10^{-6} M unlabeled test compound and were analyzed by nonlinear regression using a 4-parameter logistic equation ([Inplot] INPLOT program; [GraphPAD] GRAPHPAD Software, San Diego).--

Please reword the paragraph bridging pages 35-36 of the originally filed application as follows:

--Muscles were added to 50mL Erlenmeyer flasks containing 10mL of a pregassed Krebs-Ringer bicarbonate buffer containing (each liter) NaCl 118.5 mmol (6.93g), KCl 5.94 mmol (443mg), $CaCl_2$ 2.54 mmol (282mg), $MgSO_4$ 1.19 mmol (143mg), KH_2PO_4 1.19 mmol (162mg), $NAHCO_3$ 25 mmol (2.1g), 5.5mmol glucose (1g) and recombinant human insulin ([Humulin-R] HUMILIN-R, Eli Lilly, IN) and the test compound, as detailed below. pH at 37° was verified as being between 7.1 and 7.4. Muscles were assigned to different flasks so that the 4 muscle pieces from each animal were evenly distributed among the different assay conditions. The incubation media were gassed by gently blowing carbogen (95% O_2, 5% CO_2) over the surface while being continuously agitated at 37°C in an oscillating water bath. After a half-hour "preincubation" period, 0.5μCi of U-^{14}C-glucose was added to each flask which was incubated for a further 60 minutes. Each muscle piece was then rapidly removed, blotted and frozen in liquid N_2, weighed and stored for subsequent determination of ^{14}C-glycogen.—

Please reword the paragraph bridging pages 38-39 of the originally filed application as follows:

--Gastric emptying was measured using a modification (Plourde et al., Life Sci. 53:857-862 (1993)) of the original method of Scarpignato et al. (Arch. Int. Pharmacodyn. Ther. 246:286-295 (1980)). Briefly, conscious rats received by gavage 1.5 mL of an acoloric gel containing 1.5% methyl cellulose (M-0262, Sigma Chemical Co., St. Louis, MO) and 0.05% phenol red indicator. Twenty minutes after gavage, rats were anesthetized using 5% halothane, the stomach exposed and clamped at the pyloric and lower esophageal sphincters using artery forceps, removed and opened into an alkaline solution which was made up to a fixed volume. Stomach content was derived from the intensity of the phenol red in the alkaline solution, measured by absorbance at a wavelength of 560 nm. In most experiments, the stomach was clear. In other experiments, particulate gastric contents were centrifuged to clear the solution for absorbance measurements. Where the diluted gastric contents remained turbid, the spectroscopic absorbance due to phenol red was derived as the difference between that present in alkaline vs acetified diluent. In separate experiments on 7 rats, the stomach and small intestine were both excised and opened into an alkaline solution. The quantity of phenol red that could be recovered from the upper gastrointestinal [tact] tract within 29 minutes of gavage was 89 ± 4%; dye which appeared to bind irrecoverably to the gut luminal surface may have accounted for the balance. To compensate for this small loss, percent of stomach contents remaining after 20 minutes were expressed as a fraction of the gastric contents recovered from control rats sacrificed immediately after gavage in the same experiment. Percent gastric emptying contents remaining = (absorbance at 20 min)/(absorbance at 0 min). Dose response curves for gastric emptying were fitted to a 4-parameter logistic model using a least-squares iterative routine (ALLFIT, v2.7, NIH, Bethesda, MD) to derive ED_{50}s. Since ED_{50} is log-normally distributed, it is expressed ± standard error of the logarithm. Pairwise comparisons were performed using one-way analysis of variance and the [Student-Newman-

Keuls] STUDENT-NEWMAN-KEULS multiple comparisons test ([Instat] INSTAT v2.0, [GraphPad] GRAPHPAD Software, San Diego, CA) using $P < 0.05$ as the level of significance.--